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## The American Journal of Medicine

Vol. X JUNE, 1951 No. 6

*Editorial*

- Prevention of Rheumatic Fever . . . . . WILLIAM S. TILLET 671

*Clinical Studies*

Prophylaxis of Acute Rheumatic Fever By Treatment of the Preceding Streptococcal Infection with Various Amounts of Depot Penicillin

CAPT. LEWIS W. WANNAMAKER, CHARLES H. RAMMELKAMP, JR., MAJ. FLOYD W. DENNY, CAPT. WILLIAM R. BRINK, CAPT. HAROLD B. HOUSER, CAPT.

EDWARD O. HAHN AND JOHN H. DINGLE 673

This important paper embodies the results of large-scale, controlled observations on the prevention of acute rheumatic fever in acute streptococcal respiratory infections by prophylactic use of depot penicillin. The data indicate that the incidence of acute rheumatic fever is sharply reduced by adequate and prompt penicillin prophylaxis, that streptococci usually disappear from the oropharynx, and that there is marked inhibition of antibody (antistreptolysin) formation.

Chloramphenicol in the Treatment of Meningococcal Meningitis

FRED R. MCCRUMB, HOWARD E. HALL, ANN M. MERIDETH, GARRETT E. DEANE, JAMES V. MINOR AND THEODORE E. WOODWARD 696

The authors found chloramphenicol to be a very effective agent in the treatment of fifteen cases of meningococcal meningitis. Since chloramphenicol has also been shown to be potent in the therapy of influenzal meningitis, it is argued that this antibiotic therefore has a distinct advantage over penicillin and sulfadiazine in the urgent treatment of meningitis, particularly in infants and children in whom circumstances prevent or delay precise bacteriologic diagnosis.

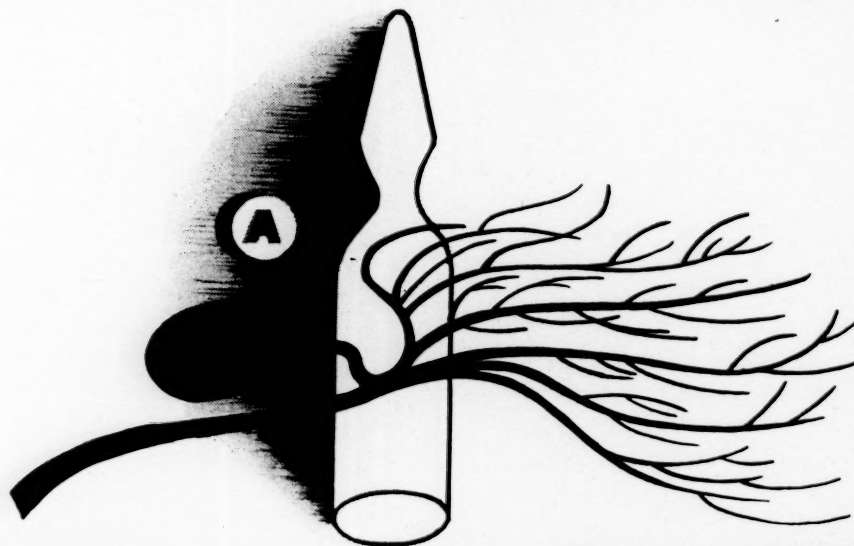
An Evaluation of the Hemagglutination Test for Tuberculosis

JACK W. FLEMING, ERNEST H. RUNYON AND MARTIN M. CUMMINGS 704

This paper presents the results of extensive trial of the Middlebrook-Dubos hemagglutination test in over 400 tuberculous and non-tuberculous subjects. Elevation of the titer may be regarded as corroboratory evidence of tuberculous infection, normal titers do not rule out active tuberculosis.

*Contents continued on page 5*





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## The American Journal of Medicine

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- Behavior of the Myocardium in Health and Disease as Studied by Coronary Sinus Catheterization . . . . . R. J. BING AND R. DALEY 711

An authoritative account of the results of coronary sinus catheterization, a new approach to the study of myocardial function notable for its ingenuity and intrepidity. While coronary sinus blood does not represent true coronary mixed venous blood, and reflects activity of left ventricular muscle only, data of the greatest interest have been obtained in normal human subjects, in anemia, thyrotoxicosis, hypertension, the failing heart, and on the effects of cardiac glycosides.

*Seminars on Pulmonary Physiology*

- Influence of Chronic Pulmonary Disease on the Heart and Circulation  
RÉJANE M. HARVEY, M. IRENÉ FERRER, DICKINSON W. RICHARDS, JR. AND  
ANDRÉ COURNAND 719

This paper provides a masterly analysis of the effects of chronic pulmonary disease, specifically emphysema, silicosis and diffusion fibrosis, upon the heart and circulation with special reference to the development of pulmonary arterial hypertension and cor pulmonale. The effects depend largely upon the relative degree of anoxia, which is often reversible, and anatomic alterations, which are often irreversible. Therapy should take these factors into account.

*Combined Staff Clinic*

- Meningitis . . . . . 739

Combined Staff Clinics (Columbia University College of Physicians and Surgeons)—This is an informal and spirited discussion of the meningitides (particularly the bacterial meningitides), with special reference to the management of meningococcal and tuberculous meningitis in their various aspects.

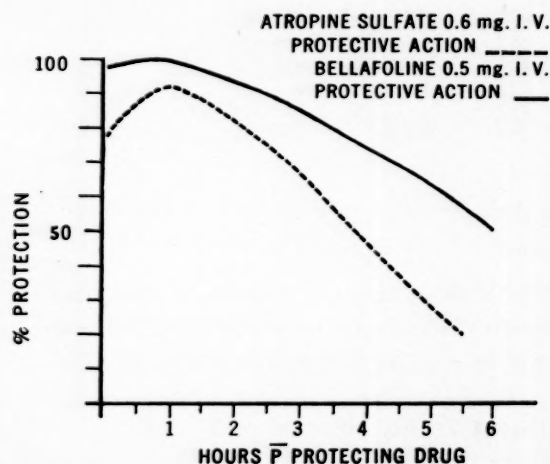
*Contents continued on page 7*

## New Form of Levorotatory Belladonna Alkaloids for Selective Spasmolytic Action

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Protecting capacity of Anticholinergic Agents against bronchospastic effects of I. V. Mecholyl. From graphs in Beakey, et al.\* *Annals of Allergy*, Vol. 7, No. 1, Jan.-Feb. 1949

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- Acute Renal Insufficiency in Man Manifesting the Arterial Necrosis Observed in Dogs Following Bilateral Nephrectomy E. E. MUIRHEAD AND ARTHUR GROLLMAN 780

Postmortem examination of a young male who died of acute renal insufficiency associated with "lower nephron nephrosis" revealed widespread arterial and arteriolar necrosis of blood vessels resembling those observed in bilaterally nephrectomized animals.

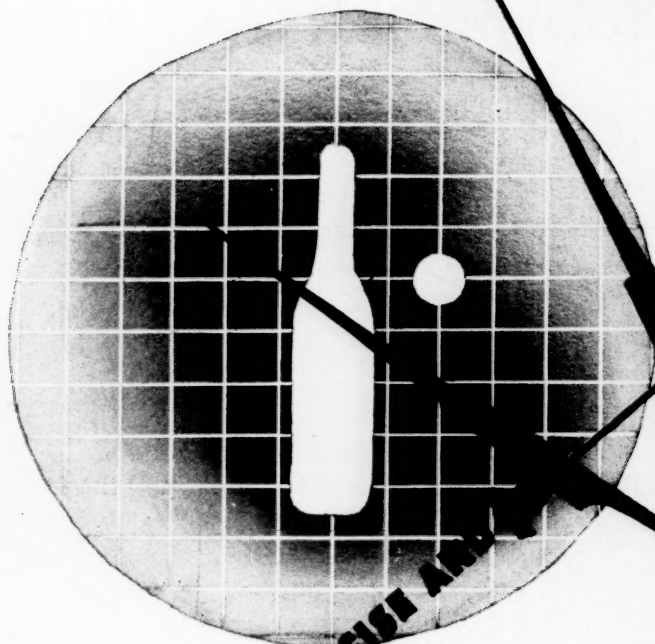
- Motor Neuritis after Tetanus Antitoxin with Involvement of the Muscles of Respiration  
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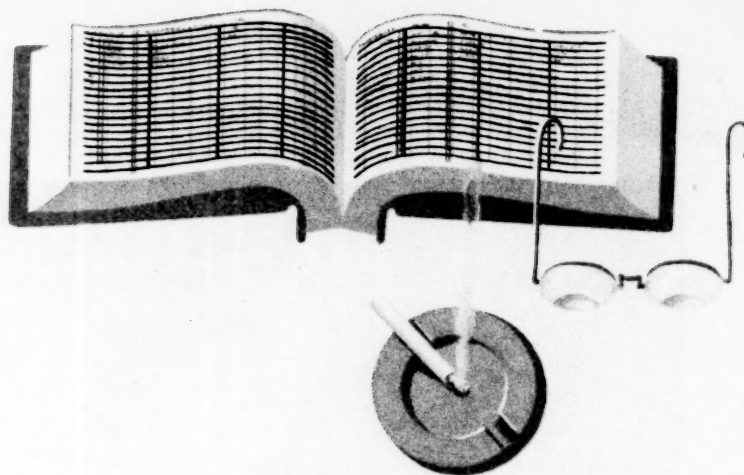
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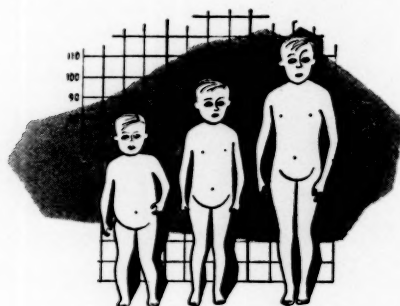
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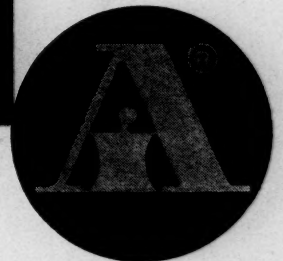
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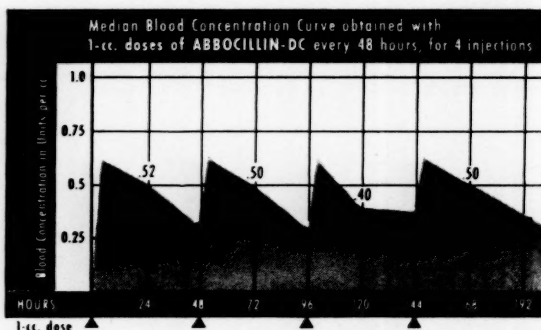
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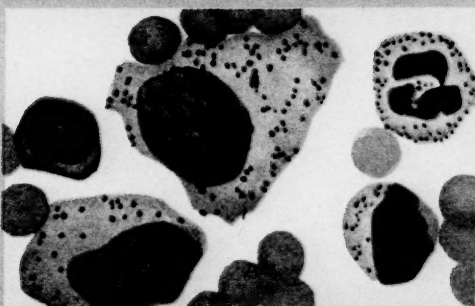
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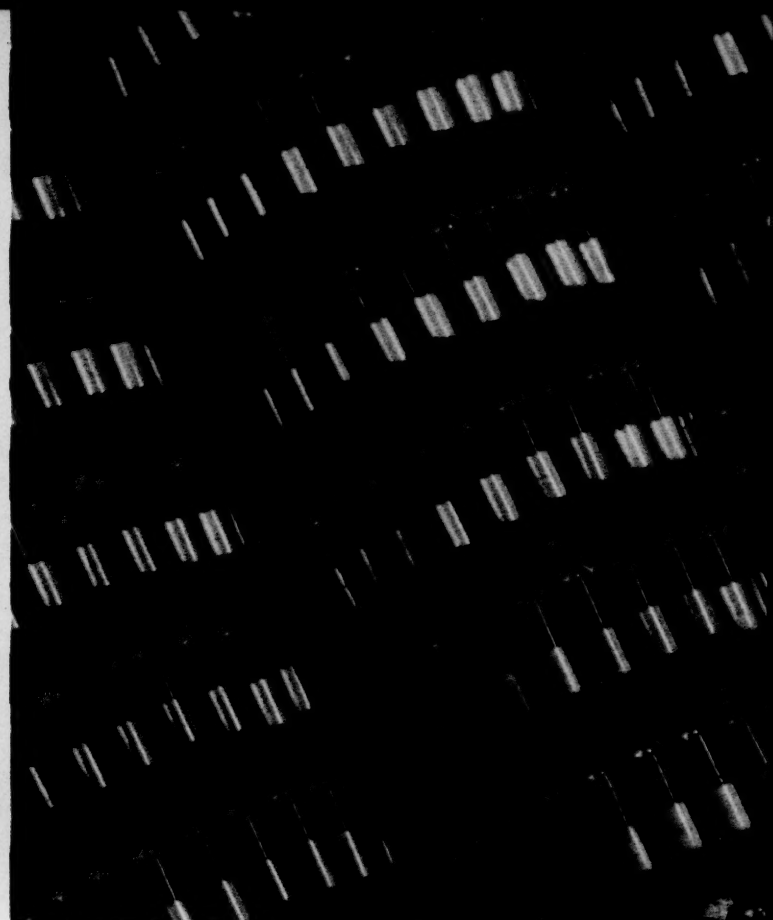
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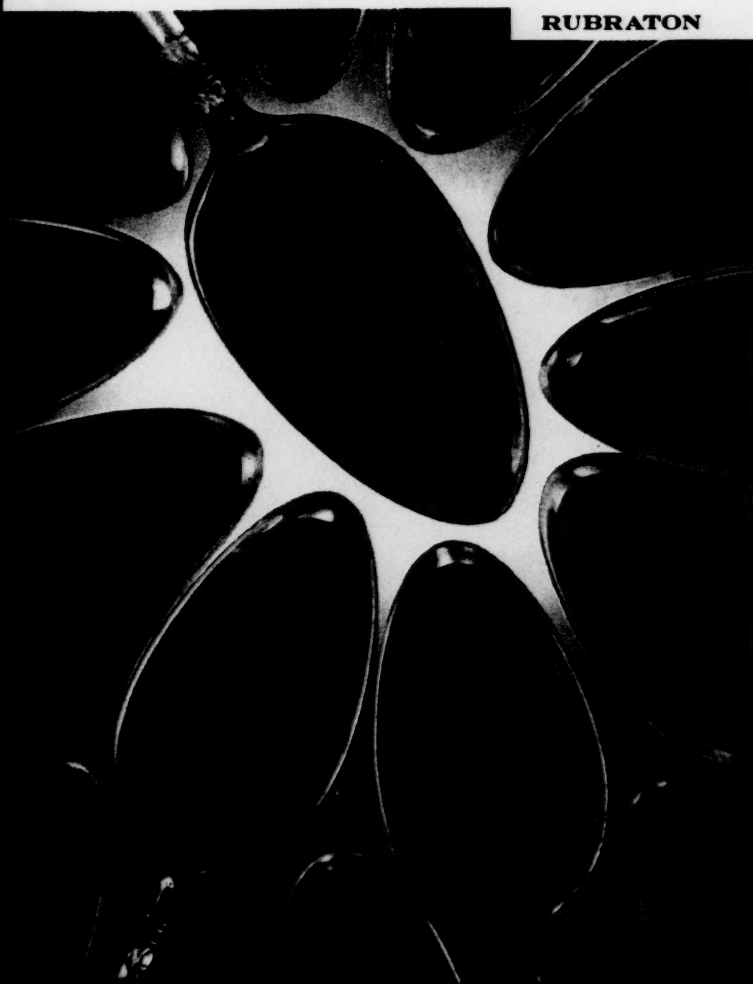


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# When anemia is on a nutritional basis...

## "critical points" of red blood cell production

### Megaloblast stage

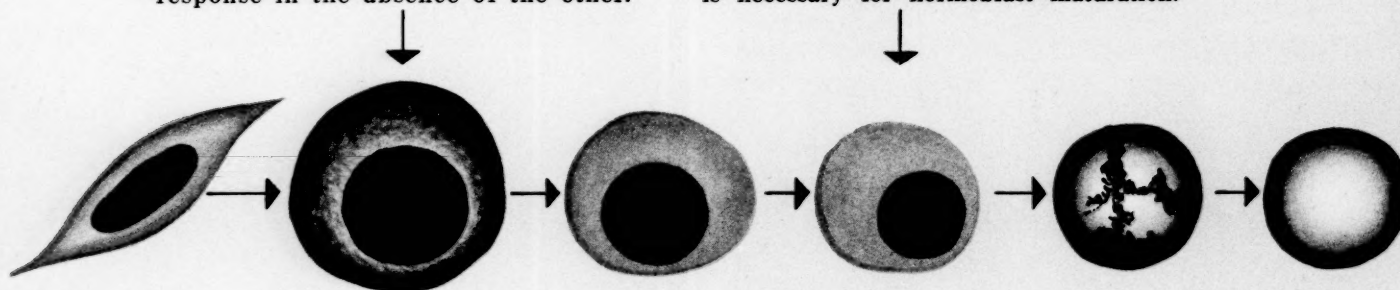
Critical Point

Both vitamin B<sub>12</sub> and folic acid are necessary for blood formation at the megaloblast stage. Neither will produce a therapeutic response in the absence of the other.<sup>1</sup>

### Normoblast stage

Critical Point

Adequate iron is necessary for normal division and growth of normoblasts and formation of hemoglobin.<sup>2</sup> Abundant vitamin C is necessary for normoblast maturation.<sup>3</sup>



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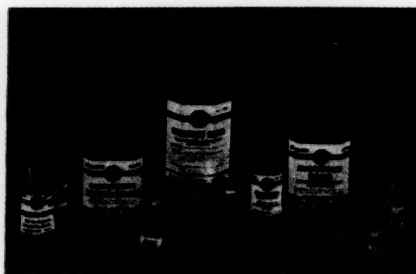
*A potent, well tolerated hematinic in an elixir that tastes good*

## RUBRAFOLIN

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*When both vitamin B<sub>12</sub> and folic acid are necessary for normal erythropoiesis*

## The Squibb RUBRA Family



1. Luhby, A. L., and Wheeler, W. E.; Health Center J. (Ohio State Univ.) 3:1, Dec. 1949.
2. Haden, R. E.; Principles of Hematology, ed. 3, Philadelphia, Lea & Febiger, 1946, p. 31.
3. Doan, C. A., and Wright, C. S., M. Clin. North America, 33:541, 1949.

...See preceding page for formula, dosage and supply for Rubraferate, Rubraton and Rubrafolin.

**SQUIBB**

# Meat . . .

## in the Low-Sodium Diet

Clinical experience<sup>1,2</sup> and investigative data<sup>3</sup> indicate that the liberal use of meat may not be contraindicated when sodium intake must be restricted. Because unsalted meat contains only relatively small amounts of sodium, while contributing importantly to other nutrient needs, meat deserves special consideration in very-low-sodium diets, in sodium-poor diets, and in no-extra-sodium diets.

Table I lists the amounts of sodium<sup>3</sup> in three kinds of meat. Table II gives the estimated amounts of sodium in hospital diets planned for cardiorenal vascular patients.<sup>4</sup>

**SODIUM IN MEAT<sup>3</sup>**

	Sodium Provided by 60 Gm. Serving	Sodium Provided by 100 Gm.
Beef, without bone	32 mg.	53 mg.
Lamb, without fat	66 mg.	110 mg.
Pork, without fat	35 mg.	58 mg.

**Table I**

**SODIUM IN HOSPITAL DIETS<sup>4</sup>**

Sodium-Poor Diets*				Very-Low-Sodium Diet†
40 Gm. Protein	70 Gm. Protein	100 Gm. Protein	130 Gm. Protein	70 Gm. Protein
400 mg. Na	500 mg. Na	800 mg. Na	1,000 mg. Na	200 mg. Na

**Table II**

\*Foods prepared and served without salt.

†Weighed diet. May contain 4 oz. of unsalted meat.

(Normal diets contain approximately 4 Gm. of sodium daily.)

Hence, the data here shown indicate that relatively generous amounts of meat may be included in low-sodium diets.

Meat serves well in the therapeutic objective of maintaining a high state of nutrition in patients with congestive heart failure or nephritic edema by providing valuable amounts of biologically complete protein and of B complex vitamins, including the recently discovered B<sub>12</sub>.

1. Wheeler, E. O.; Bridges, W. C., and White, P. D.: Diet Low in Salt (Sodium) in Congestive Heart Failure, J.A.M.A. 133:16 (Jan. 4) 1947.

2. Wohl, M. G., and Schneeberg, N. G.: Dietotherapy (Cardiovascular Disease), in Jolliffe, N.: Tisdall, F. F., and Cannon, P. R.: Clinical Nutrition, New York, Paul B. Hoeber, Inc., 1950, chap. 27.

3. Bills, C. E.; McDonald, T. C.; Niedermeier, W., and Schwartz, M. C.: Survey of the Sodium and Potassium Content of Foods and Waters by the Flame Photometer, Fed. Proc. 6:402 (Mar.) 1947.

4. Mayo Clinic Diet Manual, Philadelphia, W. B. Saunders Company, 1949, p. 113.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



**American Meat Institute**  
Main Office, Chicago... Members Throughout the United States



IVYOL, purified active principle of *Rhus toxicodendron* (1:1,000) in sterile olive oil; for *phylactic* as well as *prophylactic* use.

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Many physicians consider IVYOL injections to be most beneficial when employed *prophylactically*—for desensitizing susceptible patients early—well before the season starts. For this purpose, four injections of 0.5 cc. each are usually given at weekly intervals, beginning in the spring—or at least early enough to complete the course of four injections before patients are liable to exposure.

Experience has shown, however, that *phylactic treatment* may also be beneficial. Treatment by injection of extracts has been reported to relieve the skin eruption and to lessen the tendency to future attacks. Favorable results obtained with IVYOL included relief from itching and inflammation. Marked improvement has occurred after a single injection.

For phylactic treatment, in average cases, one

vial of IVYOL (0.5 cc.) is given intramuscularly, every 24 hours until symptoms are relieved.

*In case of unusually great severity, as shown by severe or extensive eruptions from slight exposure, the amount of active principle contained in one vial, given in one dose, might aggravate the symptoms. It is advisable, therefore, in cases of this type, to begin with an initial dose of 0.1 to 0.25 cc. Subsequent doses are increased or repeated as indicated by the reaction.*

*For complete information see circular accompanying product.*

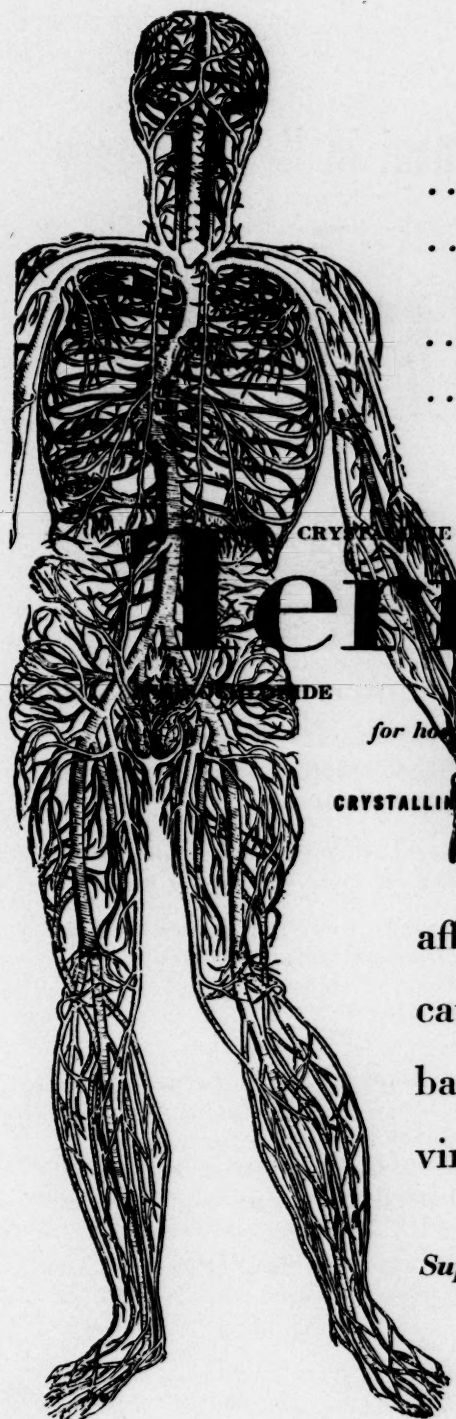
Sharp & Dohme, Philadelphia 1, Pa.

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...when oral therapy is not feasible  
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CRYSTALLINE TERRAMYCIN HYDROCHLORIDE FOR INTRAVENOUS INJECTION

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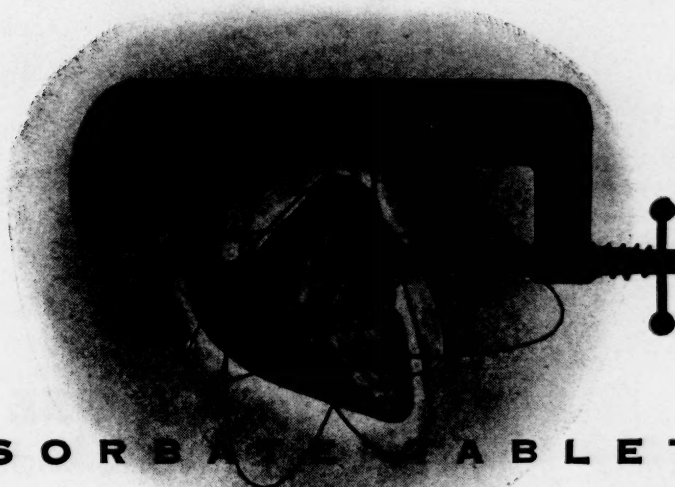
MYOCARDONE is *now* available at your prescription pharmacy. Give your next cardiac patient the benefit of this new *proven* treatment.

Myocardone 1½ gr. tablets are supplied in bottles of 100. Suggested dosage—2 or 3 tablets t. i. d.

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are responsible for greater demands  
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The clinical manifestations of adrenal exhaustion  
are usually asthenia, hypotension and/or disturbed  
water balance.



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**CORTISORBATE** provides the life-maintaining principle of the adrenal cortex in oral form for greater patient acceptance and cooperation.

**Dosage:** 1 to 3 Oral Rat Units per day — in divided doses at convenient intervals — usually produce satisfactory results. Used preoperatively to prevent surgical shock. 3 to 6 Oral Rat Units per day over two to three weeks.

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CHLOROMYCETIN's world-wide reputation stems from its ability to produce rapid, clinical response in a wide variety of infectious diseases — bacterial, viral and rickettsial. Numerous reports and the experience of daily practice confirm its

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Dehydrocholic Acid ..... ½ grain  
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Extract of Ox Bile, U.S.P. .... 1 grain  
Sorbitan Monooleate Polyoxyethylene  
Derivative ..... 2½ grains  
Oleic Acid, U.S.P. .... 2½ grains

**DOSAGE:** One to two capsules three times a day or as directed by the physician.

**SUPPLY:** In bottles of 100 capsules.

**REF.:** 1) Jones, C. M., et al.: Ann. Int. Med. 29:1-10, July 1948  
2) Becker, G. H., et al.: Gastroenterology 14:80-91, Jan. 1950

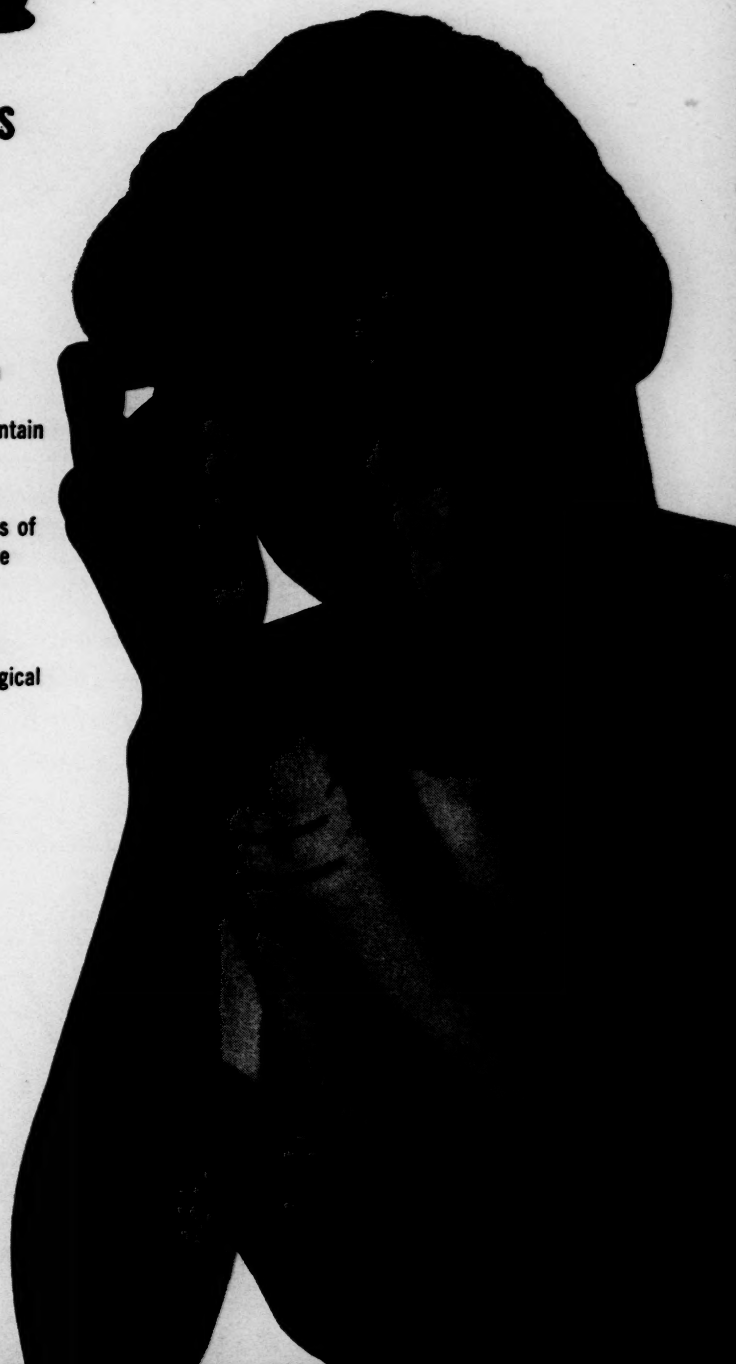
If you would like to receive copies of our gallbladder diet sheets for use with Oxsorbil Capsules, clip and mail this coupon:

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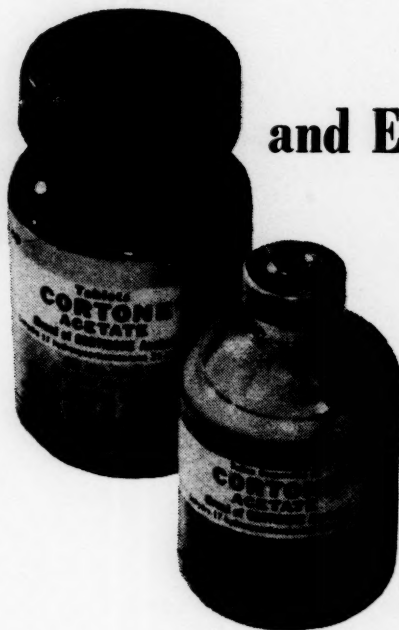
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*supplementary effects*  
*wherever estrogen-androgen therapy is indicated...*

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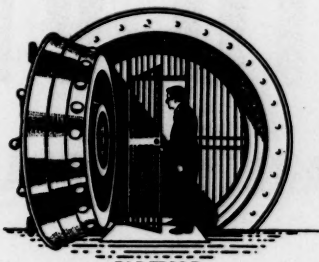
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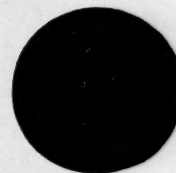


**Normal.** Capillaries clearly defined; no transudation, hemorrhage, or papilledema.



RUTAMINAL\* provides the extra protection of rutin and ascorbic acid...in support of the cardiotonic action of aminophylline, and the sedation of phenobarbital.

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*Whenever aminophylline and phenobarbital are indicated...*

\*RUTAMINAL is a trademark of Schenley Laboratories, Inc., and designates exclusively its brand of tablets containing rutin, ascorbic acid, aminophylline, and phenobarbital.

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Dilates the coronary arteries without appreciable effect on peripheral circulation—does not alter blood pressure •

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**Ammivin** is the preferred dosage form of khellin •

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potent coronary  
vasodilator*



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"'Dexedrine' Sulfate, administered orally after surgery of the eye, ear, nose and throat . . . results in earlier ambulation, shortens hospitalization and hastens postoperative recovery," according to a recently published paper.<sup>1</sup>

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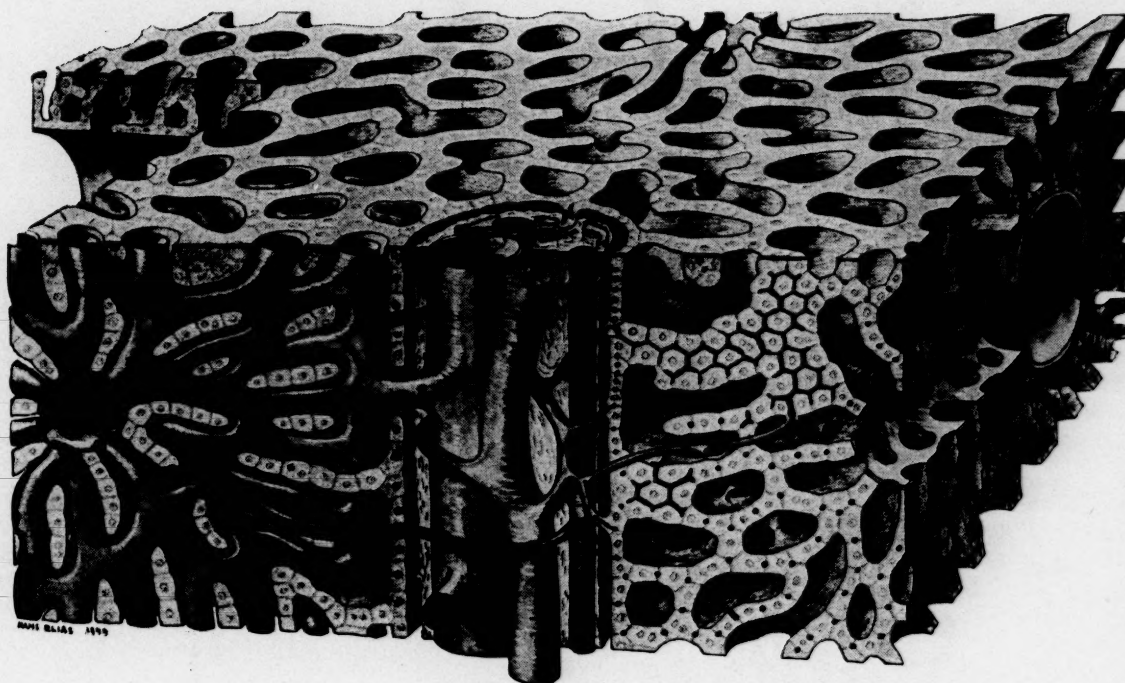
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1. Barnett, S.E.: *Eye, Ear, Nose & Throat Monthly* 39:19, 1950.

\*T.M. Reg. U.S. Pat. Off.



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RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**





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The nutritional contribution of three servings of Ovaltine in milk (the recommended daily amount) is defined in the appended table.

1. Bortz, E. L.: Management of Elderly Patients, Postgraduate Med. 3:186 (Mar.) 1950.

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# Ovaltine

Three servings of Ovaltine, each made of  
1/2 oz. of Ovaltine and 8 oz. of whole milk,\* provide:

PROTEIN . . . . .	32 Gm.	VITAMIN A . . . . .	3000 I.U.
FAT . . . . .	32 Gm.	VITAMIN B <sub>1</sub> . . . . .	1.16 mg.
CARBOHYDRATE . . . . .	65 Gm.	RIBOFLAVIN . . . . .	2.0 mg.
CALCIUM . . . . .	1.12 Gm.	NIACIN . . . . .	6.8 mg.
PHOSPHORUS . . . . .	0.94 Gm.	VITAMIN C . . . . .	30.0 mg.
IRON . . . . .	12 mg.	VITAMIN D . . . . .	417 I.U.
COPPER . . . . .	0.5 mg.	CALORIES . . . . .	676

\*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

*the character of  
response depends on  
the specificity of  
the hormone*

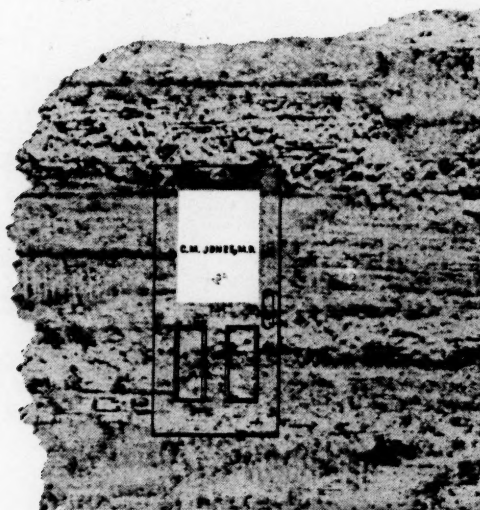
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- is completely safe. 'Cologel' lacks the danger of producing an esophageal obstruction, and the possibility of an intestinal impaction following its use is minimized.
- is indicated for the treatment of chronic or acute constipation of adults and children in the absence of organic diseases.

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*How supplied:* In 8-ounce and one-pint bottles.



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## Editorial

### Prevention of Rheumatic Fever

**T**HERE appears in this issue of *The American Journal of Medicine* an article on the "Prophylaxis of Acute Rheumatic Fever by Treatment of the Preceding Streptococcal Infection with Various Amounts of Depot Penicillin" that is of special interest. Documentation of the reported observations is given in detail. In addition, the findings have fundamental implications for a substantial reduction in the occurrence of rheumatic fever and its associated heart disease. For this latter reason it particularly merits special comment.

It must be apparent that the greatest contribution to the problems of rheumatic heart disease will and must come from its prevention. Any contribution, therefore, to this phase of the subject of rheumatic fever should receive the widest dissemination since a practical measure is at hand that, if employed by physicians properly and extensively, can have a significant effect on a disease of great clinical importance.

In its simplest terms the report indicates that when acute attacks of streptococcal tonsillitis and nasopharyngitis were treated properly with penicillin, the reduction in the incidence of rheumatic fever during the subsequent forty-five days of observation amounted to two established cases in the treated group of approximately 1,000 as contrasted with twenty-eight proven cases in the control group not receiving penicillin, also numbering approximately 1,000. It is variously estimated, depending on geographical areas, that 3 to 5 per cent of cases of acute streptococcal respiratory infections are followed with the appearance of the stigmas of rheumatic fever. In rough figures, therefore, it is not unreasonable to envision that if ideal conditions for the treatment of acute streptococcal respiratory infections in the civilian population could

be brought into use, an approximate fifteenfold reduction in cases of rheumatic heart disease could be accomplished annually.

The two major factors in the study conducted at the Francis E. Warren Air Force Base, Wyoming, were (1) the assumption that all patients having exudate on the tonsils or pharyngeal wall were of beta hemolytic streptococcal etiology and (2) the administration parenterally of at least 1,200,000 units of penicillin within ninety-six hours.

The frequency of the correctness of the bacteriologic diagnosis as determined by cultures and serologic tests is given in the body of the article.

Perhaps the greatest difficulties that are presented for the proper and widespread application of the procedures to civilian medicine are involved in the infrequency of household bacteriologic diagnoses and in the mildness of some pre-rheumatic infections that do not require or receive professional medical care. However, if every physician took a point of view comparable to that used by the study group of the Streptococcal Disease Laboratory, namely, that all cases with exudate were probably of streptococcal origin, then neither the absence of bacteriologic cultures nor delay in obtaining the results of cultures when taken would deter initiation of effective treatment. In accomplishing the desired prophylaxis it would appear rational also to administer the appropriate injections of penicillin, during the periods of the year of greatest incidence of streptococcal pharyngitis, to acute infections, particularly within the pediatric and young adult age groups, even with less definite signs of hemolytic streptococcal disease than the exudative features mentioned previously.

Furthermore, it is of special importance to recognize the fact that recurrences of acute respiratory infections may and do occur in the same individual within a single season or, more commonly, during succeeding years over extended periods of time. Consequently consciousness is required on the part of physicians of recognizing that the effectiveness of treatment must be a continuous one through the years, and the sustaining impetus for continued application of the therapy may be derived from awareness of the fact that substantial reduction in permanent heart disease of the young is the reward.

In another type of cardiovascular disease there is an additional example of the value of prevention as a highly effective means of dealing with problems of permanent cardiac damage. There is every prospect that prompt and adequate treatment of chancre with penicillin can reduce substantially the subsequent development of syphilitic heart disease. The interval of time between the occurrence of chancre and clinical manifestations of cardiovascular involvement may be longer than the period between the initiation of proper antibiotic treatment and present time. Consequently comprehensive statistical data are not yet possible. However, it seems unequivocal that if the total spirochaetal population is abolished at the superficial chancral stage of the infection it must follow that no delayed complications will subsequently occur.

In connection with civilian activities designed to raise funds, large amounts of publicity are correctly and constantly given to the importance of heart disease and the need for study and research in order to ameliorate effectively the consequences of its high incidence in the total population. Large grants of funds are made to medical institutions for studies in this field. Medical literature abounds in articles con-

cerned with physiologic studies of heart disease after it is established.

The hemodynamics of the circulation; forward failure versus backward failure; the electrolyte balance in relation to renal function; salt retention first, followed with renal impairment or renal insufficiency first, followed with depressed excretion of salt; and proportional degrees and types of disturbances of electrical myocardial conduction constitute conspicuous categories of investigation after heart disease is established.

Among students of these physiologic, biochemical and biophysical abnormalities the interpretation of data varies and is subject to conflicting opinions. In the opinion of this author a not inconsiderable amount of the controversy belongs in the category of which came first the hen or the egg, after heart disease is established.

By contrast, the approach to the problem of rheumatic heart disease—and also syphilitic heart disease—illustrated by studies directed toward their prevention can and should take decisive priority in any broadscale effort to attack the subject of heart disease.

The studies of Wannamaker, Rammelkamp and associates are sufficiently well documented to demonstrate the high probability of their essential correctness, and it now remains to introduce comparable measures into civilian medical practice in order to adjust procedures according to situations peculiar to civilian life.

Finally, the conditions under which the studies on the prevention of rheumatic fever were conducted merit special notice since they are illustrative of the fruitfulness of results that have been obtained through the combined efforts of military and civilian scientific and administrative personnel in organizing and pursuing investigations of a subject of great mutual importance.

WILLIAM S. TILLET, M.D.



# Clinical Studies

## Prophylaxis of Acute Rheumatic Fever\*

*By Treatment of the Preceding Streptococcal Infection with Various Amounts of Depot Penicillin*

CAPT. LEWIS W. WANNAMAKER, M.C., CHARLES H. RAMMELKAMP, JR., M.D.,  
MAJ. FLOYD W. DENNY, M.C., CAPT. WILLIAM R. BRINK, M.C.,  
CAPT. HAROLD B. HOUSER, M.C., CAPT. EDWARD O. HAHN, M.C.

*Francis E. Warren Air Force Base, Wyoming*

*and JOHN H. DINGLE, M.D.*

*Cleveland, Ohio*

PRELIMINARY studies from two groups of investigators<sup>1,2</sup> indicate that the treatment of acute streptococcal respiratory infections with penicillin will prevent the subsequent development of rheumatic fever. The investigations on the prophylaxis of rheumatic fever at the Streptococcal Disease Laboratory<sup>2</sup> have been extended to include the evaluation of three different dosage schedules of depot penicillin in a controlled series of 2,340 patients with exudative tonsillitis and pharyngitis. The purpose of the present report is to describe the effects of such treatment on the incidence of acute rheumatic fever, the streptococcal carrier state and the immunologic response of the host.

The study was conducted between January 24, 1949, and February 22, 1950, at Francis E. Warren Air Force Base in southeastern Wyoming. This installation is composed of technical training schools which receive as students enlisted men who have just completed twelve weeks of basic training at a southwestern base and a few seasoned airmen from other installations. The duration of the courses of instruction varies from eight to thirty-four weeks. Students registered in the schools comprise about 60 per cent of the population; the remainder consists of the permanent party which includes instructors and maintenance personnel.

The strength of the base during the period of the study was approximately 8,000. Since there

was an average turnover of 1,000 men per month, it is estimated that a total of 21,000 airmen were stationed at this air force base during the period of study.

### METHODS

*Selection of Cases and Routine Studies.* All soldiers reporting to sick call with respiratory symptoms who showed either exudative tonsillitis or pharyngitis or an oral temperature of 100°F. or greater were admitted to the hospital. Within a few hours after admission each patient was examined by a member of the professional staff of the laboratory. In addition to identifying data a standardized history and physical examination were recorded. A total leukocyte count, culture of the tonsils and oropharynx, and specimen of serum were obtained.

Only those patients who exhibited exudative lesions on the tonsils or oropharynx were included in the study group. Five patients with exudative tonsillitis and concomitant rheumatic fever were excluded. Treatment was determined by air force serial number; those patients whose serial number ended in an even digit received intramuscular injection of crystalline procaine penicillin G in peanut or sesame oil containing 2 per cent aluminum monostearate. All injections of penicillin were administered by a member of the professional staff. Patients whose serial number ended in an odd digit received no

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specific treatment and served as controls. The distribution of cases according to the three dosage schedules used is recorded. (Table I.)

Patients in the treated groups remained in the hospital until the prescribed course of penicillin therapy had been completed. Discharge of

TABLE I  
DISTRIBUTION OF CASES OF EXUDATIVE PHARYNGITIS  
AND TONSILLITIS ACCORDING TO TREATMENT

Penicillin* Dosage (Units)	Inclusive Dates	No.		Totals
		Treated	Untreated	
I. 300,000 stat. 300,000 48 hr. 600,000 96 hr.	Mar. 3, 1949– Sept. 15, 1949	634	582	1,216
II. 300,000 stat. 300,000, 72 hr.	Jan. 24, 1949– Mar. 2, 1949	254	288	542
III. 600,000, stat.	Sept. 16, 1949– Feb. 22, 1950	290	292	582
	Totals	1,178	1,162	2,340†

\* Procaine-penicillin G in peanut or sesame oil containing 2 per cent aluminum monostearate.

† In addition to the cases recorded there were fifty-five patients with exudative lesions who were given penicillin (either crystalline penicillin or a combination of crystalline and depot penicillin) in miscellaneous dosages by the attending ward physician. These cases were excluded from the analysis since the dosage and duration of therapy varied considerably, treatment was usually delayed and most of the patients were treated because of the severity of the illness or the presence of a suppurative complication. Of the fifty-five cases the serial number was odd in forty-three instances, even in twelve. One case of rheumatic fever developed in this group. In this instance treatment was instituted thirty-two hours after the onset of exudative tonsillitis and otitis media; rheumatic fever developed fifty-seven days later. Penicillin was given in doses of 100,000 units every six hours for a total dose of 1,500,000 units.

treated and control patients to an active duty status was usually effected on the fifth or sixth hospital day.

A follow-up observation was made twenty-one to thirty-five days after admission to the hospital. For various reasons a few examinations were conducted before the twenty-first or after the thirty-fifth day. At this time a throat culture and a convalescent serum specimen were obtained. Without knowledge of the serial number or therapy administered, a member of the professional staff recorded symptoms of pain or swelling of the joints, feverishness, skin rash or sore throat. Those patients presenting symptoms were examined and an electrocardiogram and sedimentation rate obtained. All patients suspected of having acute rheumatic fever were hospitalized on a special study ward.

Patients admitted to the rheumatic fever study ward remained until a diagnosis was established. In addition to the routine history and physical examination, symptoms and physical signs were recorded daily for the first week

and at weekly intervals thereafter. Pulse and rectal temperatures were recorded every four hours. Sedimentation rates were obtained three times each week and total leukocyte counts twice each week. Electrocardiograms were recorded daily during the first week of hospitalization or during the febrile period and at least weekly thereafter. Cultures of the throat and blood specimens were taken at ten-day intervals until the patient was discharged.

**Laboratory Methods.** Laboratory studies at the time of the acute infection, at the time of follow-up examination and at the time of hospitalization for suspected rheumatic fever were performed in a standard manner. Throat swabs were returned immediately to the laboratory and streaked within one hour on the surface of an agar plate containing horse blood. A stab was made into the agar through the streaks to determine the type of sub-surface hemolysis.<sup>3</sup> After incubation at 37°C. for eighteen hours the plates were examined for colonies exhibiting beta-hemolysis. Selected colonies were then transferred to sheep blood agar plates for isolation in pure culture. Streptococci producing beta-hemolysis on the surface or in the stab on sheep blood agar plates were classified according to the methods of Maxted,<sup>4</sup> Fuller,<sup>5</sup> and Swift, Wilson and Lancefield.<sup>6</sup>

Sera were stored at -20°C. Antistreptolysin "O" titers on all sera from each patient were performed simultaneously according to a modification of the method of Hodge and Swift.<sup>7</sup> A difference of two dilution increments was considered to be beyond the technical error of the test and diagnostic of a streptococcal infection. Sedimentation rates were performed according to the method of Westergren.<sup>8</sup>

**Diagnosis of Rheumatic Fever.** The diagnosis of the non-suppurative complication,\* rheumatic fever, was according to a modification of the classification of Jones.<sup>9</sup> With few unavoidable exceptions the final classification of each patient was made without knowledge of treatment during the preceding illness of exudative tonsillitis or pharyngitis.

An illness was classified as acute rheumatic fever if there were two major manifestations or one major and two minor manifestations. (Table II.) The diagnosis of possible rheumatic fever was made when there were one major and one minor, one major or two minor manifesta-

\* No instance of acute glomerulonephritis was encountered.



tions. Epistaxis was not included as a minor manifestation since it is common at this altitude. Abdominal pain, pulmonary changes and anemia were encountered but were not required in the classification of the patients studied. In

as compared to the acute phase specimen was demonstrated in 68.4 per cent of the patients in the untreated groups. These data indicate that most of the infections observed were caused by group A streptococci although, as will be dis-

TABLE II  
CLINICAL AND LABORATORY FEATURES USED IN THE DIAGNOSIS OF RHEUMATIC FEVER

Manifestations	Remarks
Major:	
1. Carditis	
A. Definite cardiac enlargement	Demonstration of a change in the size of the heart
B. Appearance of a significant heart murmur	An easily heard mitral systolic murmur transmitted toward axilla, or a mitral or aortic diastolic murmur
C. Pericardial friction rub	
D. Heart block	A P-R interval of 0.21 seconds or greater or second or third degree heart block
E. Cardiac failure	
2. Migrating polyarthritides	The objective finding of one or more of the following in more than one joint: tenderness, redness, swelling and heat
3. Recurrences of rheumatic fever	A reliable history or the presence of rheumatic heart disease
4. Chorea	
5. Subcutaneous nodules	
6. Erythema marginatum*	
Minor:	
1. Fever	Rectal temperature over 100°F.
2. Polyarthralgia	No objective findings present
3. Elevated erythrocyte sedimentation rate	20 mm. per hour or above by the Westergren method
4. Abnormal T waves on electrocardiogram	Only changes in leads I or CF <sub>4</sub> on serial electrocardiograms considered
5. Abdominal pain	Instances of 5, 6, 7 and 8 encountered but did not contribute to the classification of these patients
6. Epistaxis	
7. Pulmonary changes	
8. Anemia	

\* In a previous paper<sup>3</sup> this was considered a minor manifestation.

this particular group no instance of chorea or subcutaneous nodules was observed.

#### ETIOLOGIC NATURE OF OBSERVED INFECTIONS

At the time these studies were instituted streptococcal infections were epidemic. However, the data were examined to determine whether in this particular study the presence of exudate on the tonsils or pharynx could be considered a reliable indication of a streptococcal infection. The history and physical findings were in most instances typical of streptococcal infection as reported in a more detailed analysis of the clinical course of a sample from this study.<sup>10</sup> The isolation of group A streptococci from the admission throat culture of 75.7 per cent and a total leukocyte count of 12,000 or higher in 63.8 per cent of patients lend further support to the streptococcal etiology of these infections. Finally, a diagnostic increase in the antistreptolysin titer of the convalescent serum

cussed subsequently, the relative proportion of streptococcal infections to non-streptococcal infections changed during the course of the study.

#### COMPARABILITY OF TREATED AND CONTROL GROUPS

The treated and control groups of patients during each particular treatment schedule were comparable with certain minor exceptions. (Table III.) In each schedule the number of patients who gave a history of rheumatic fever in the past was slightly greater in the control than in the treated groups. In schedules II and III there was also a somewhat higher incidence of a history of a previous heart murmur in the control group.

It is apparent from examination of Table III that during the course of these studies there was a change in the population as well as in the type of streptococcus causing the infections. Treat-

ment was instituted at about the same time after the onset of illness in each of the three schedules although during schedule I the patients received treatment somewhat earlier than patients included in schedules II and III.

## RESULTS

*Treatment According to Schedule I.* The prophylactic effect of a total dose of 1,200,000 units of depot penicillin administered in three intramuscular injections was determined in a group

TABLE III  
COMPARABILITY OF THE TREATED AND UNTREATED GROUPS

	Treatment Schedule					
	I		II		III	
	Treated (%)	Control (%)	Treated (%)	Control (%)	Treated (%)	Control (%)
Age 17 to 20 yr. ....	82.9	80.9	87.2	90.2	72.8	72.9
Previous history of:						
Rheumatic fever. ....	2.2	2.6	2.4	2.8	1.4	1.7
Heart murmur. ....	1.7	1.4	2.0	2.4	4.5	5.8
Tonsillectomy. ....	25.7	30.6	28.0	28.8	23.8	22.9
Confluent exudate. ....	7.7	6.0	7.1	4.5	9.3	8.6
Leukocyte count, 12,000 or over on admission. ....	65.2	71.5	60.9	58.9	60.8	56.6
Group A streptococci on admission throat culture. ....	78.4	85.6	66.5	66.9	70.7	71.6
Type distribution of group A streptococci						
Type 5. ....	26.3	28.4	24.0	20.8	12.2	15.3
Type 14. ....	40.9	33.1	15.6	19.8	53.2	48.3
Type 24. ....	16.7	19.8	49.1	43.8	8.8	7.2
Antistreptolysin titer of 125 or less on admission. ....	68.4	70.1	76.3	67.4	66.0	70.7
Time of treatment after onset:						
Less than 24 hr. ....	27.8	....	26.0	....	23.8	....
24 to 47 hr. ....	45.7	....	46.5	....	41.0	....
48 to 71 hr. ....	19.2	....	16.1	....	18.3	....
Greater than 72 hr. ....	7.3	....	11.4	....	16.9	....
Follow-up obtained. ....	81.4	83.7	78.7	83.0	90.3	92.5

From all the available evidence, which includes isolation of group A streptococci on admission to the hospital and elevated leukocyte counts, it appears that while schedule I was used most of the infections were caused by group A streptococci. This was confirmed by the fact that 76 per cent of the control patients in this schedule developed an increased titer of antistreptolysin. In contrast, an increase in antibodies was demonstrated in the paired sera of 63.5 per cent of the controls in schedule II, and 59.5 per cent of the controls in schedule III. These antibody studies, along with the decreased number of isolations of group A streptococci and low leukocyte counts, indicate that an appreciable number of patients studied during schedules II and III had non-streptococcal exudative pharyngitis or tonsillitis.\*

\* Since in approximately 80 per cent of patients with

of 1,216 patients with exudative tonsillitis or pharyngitis. Of this group 634 were treated and 582 served as controls. (Table I.) Follow-up examinations were obtained in 82.5 per cent of the total group, indicating that at least this proportion of the total group remained on this base during the period that non-suppurative complications usually develop. In a total of twenty-eight patients an illness classified as rheumatic fever or possible rheumatic fever developed. In addition there were twenty-seven patients who at follow-up examination gave a history of joint pains (with or without other symptoms) but were found to have no other

streptococcal infections antistreptolysin develops during convalescence, it may be estimated that 4, 17 and 21 per cent of patients studied in schedules I, II and III, respectively, did not have streptococcal exudative tonsillitis or pharyngitis.



stigmas of rheumatic fever. The distribution between treated and control groups of the aforementioned patients who exhibited symptoms or signs of a non-suppurative complication of the observed attack of tonsillitis or pharyngitis is shown in Table iv.

The data in Table iv show that definite rheumatic fever occurred seven times more frequently in the untreated patients than in those who received penicillin. Furthermore, there appeared to be a significant difference between the incidence of joint symptoms in the two groups since eight patients had joint pains in the treated group while nineteen complained of joint pains in the control group.

The characteristics of the acute respiratory illness and the subsequent attack of rheumatic fever or possible rheumatic fever are tabulated in Table v. The cases are arranged according to the time interval between the observed attack of exudative tonsillitis or pharyngitis and the onset of rheumatic fever. During schedule i the time interval varied from eight to 110 days.

Because of the wide variation in the time interval before the onset of symptoms of rheumatic fever the data were analyzed to determine whether there was any difference in those patients with a short and those with a long time interval. A difference was demonstrated when a comparison was made between the type of streptococcus isolated at the onset of the observed respiratory infection and the type isolated on admission for the rheumatic fever episode. No change in type was observed in seventeen patients in whom the interval between the onset of the two diseases was twenty-eight days or less. In contrast, of eleven patients whose first symptom of rheumatic fever began twenty-nine days or later after the onset of the respiratory infection, a change in type was definitely established in six instances. From an additional case in this group, P-2457, a type 23 streptococcus was isolated at follow-up examination on the twenty-fifth day, whereas a type 14 organism was isolated at the time of admission for the observed respiratory infection and again thirty-five days later at the time of admission for rheumatic fever.

In twenty-three of the twenty-eight patients there is little doubt that the observed respiratory infection was caused by the streptococcus since a diagnostic increase in the antistreptolysin titer was demonstrated in the convalescent blood specimen. The details of the four cases (P-1932,

P-2461, P-2311 and P-2371) in which a diagnostic increase in the antibody titer did not occur and one case (H-338) in which an acute titer was not available follow:

Case P-1932 became ill at 9 P.M. on March 29, 1949. On examination on March 30th there was

TABLE IV  
NON-SUPPURATIVE SEQUELAE DEVELOPING  
IN 1,216 PATIENTS OBSERVED DURING  
PENICILLIN THERAPY, SCHEDULE I

Classification	No. of Patients	
	Treated (634)	Control (582)
Definite rheumatic fever . . . . .	3	22
Possible rheumatic fever . . . . .	1*	2†
Other‡		
Joint pains . . . . .	5	16
Joint pains and swelling . . . . .	1	2
Joint pains and feverishness . . . . .	2	..
Joint pains, swelling and feverishness . . . . .	..	1
Totals	12	43

\* This case, P-2371, was thought to be a penicillin reaction.

† One of these cases (H-338) was thought to be rheumatoid arthritis.

‡ Exclusive of the first two diagnostic categories.

discrete exudate on the tonsils and the lymph nodes were enlarged and tender. The leukocyte count was 14,200. The throat culture on admission showed no beta-hemolytic colonies, but on the subsequent two days numerous type 14 streptococci were isolated. The acute phase antistreptolysin titer was 200 and thirteen days later it was 250. The symptoms of rheumatic fever developed twelve days after the onset of the observed respiratory illness.

From the laboratory and clinical evidence this illness should be considered a streptococcal infection. The small rise in antistreptolysin titer may have been due to the short interval between the two serum specimens.

In case P-2461 there was no increase in the antistreptolysin titer but the initial titer of 400 was elevated. In this instance a rise of at least 100 units was required before an increase in antibody could be detected. The acute illness was characterized by discrete exudate on the tonsils and by enlarged, tender cervical lymph

nodes. The total leukocyte count was 12,000 and a profuse growth of type 14 streptococci was obtained on culture. These data indicate that this infection was caused by group A streptococci.

In case H-338 the leukocyte count was 9,000 and type 14 streptococci were isolated from the culture in small numbers. An acute phase blood was not available for antibody determinations but there was an increase in the antistreptolysin titer from 317 on the thirty-second day to 400 on the forty-fifth day after the onset of exudative tonsillitis. It appears possible that this attack of exudative tonsillitis was not caused by the streptococcus and that there was an intervening infection caused by type 24 streptococci since this organism was isolated on admission for rheumatic fever. This patient was thought to have rheumatoid arthritis but because of multiple joint pains, fever and an increased sedimentation rate the illness was classified as possible rheumatic fever.

The last two (P-2311 and P-2371) of the five illnesses about which there was some doubt as to the streptococcal etiology of the observed attack of exudative tonsillitis are discussed later.

Since penicillin was demonstrated to be an effective drug in preventing rheumatic fever, a detailed history is presented of the four patients (P-2311, P-2371, P-2457 and H-499) in whom the disease developed following such therapy.

Case P-2311, aged eighteen, entered the hospital on March 30, 1949, giving a history of onset at 6:00 A.M., March 26th, of malaise, headache, feverishness and sore throat. Examination showed a small amount of exudate on the superior pole of the right tonsil and some redness of the surrounding tissues. The cervical nodes were enlarged and tender bilaterally. The temperature was 100.6°F. The patient was started on penicillin therapy four days after the onset of the infection.\* The only complaint on the second hospital day was sore throat, and two small ulcers measuring 4 mm. in diameter were observed on the right anterior pillar. On the third day the patient was symptomatically well. No fever was demonstrated after the initial temperature of 100.6°F.

The total leukocyte count was 10,500 on admission and 9,700 on the second day. Throat cultures taken on the first two hospital days failed to show beta-hemolytic streptococci.

\* Through error this patient was reported previously<sup>2</sup> as having received penicillin seventy-two hours after the onset of the illness.

This patient had chorea and acute rheumatic fever at the age of seventeen. He had been told that he had a heart murmur.

Following discharge from the hospital and about twenty-one days from onset of tonsillitis, he began to notice vague pains in the feet, knees, elbows and shoulders, and complained of chest pain on the right side. The culture taken on follow-up examination on April 21st showed group A streptococci which were classified as questionable type 5. The antistreptolysin titers of the blood taken on the third and twenty-fourth day after onset of the respiratory illness were 159 and 200, respectively. The patient entered the hospital on the thirty-fourth day because of arthralgia and fever. The throat culture on the next day showed a predominant growth of group A, type 5 streptococci and the antistreptolysin titer was now 250. By the forty-seventh day the titer was 500. He remained in the hospital nine months and showed type 5 streptococci on most cultures. The illness was characterized by fever of 100° to 102°F. throughout. A mitral systolic murmur was heard at all examinations and after two months aortic and mitral diastolic murmurs developed.

In summary then this patient's acute respiratory illness on the first admission may not have been caused by the streptococcus. The ulcerations were unusual and the degree of rise in antibody during the first twenty-four days was slight. Treatment with penicillin was not instituted until the fourth day of illness. The fact that a possible type 5 streptococcus was isolated on the twenty-fourth day and a type 5 was subsequently found throughout the rheumatic fever episode suggests that the initiating streptococcal infection was acquired after penicillin therapy of the observed attack of exudative tonsillitis had been discontinued.

Case P-2371 was classified as possible rheumatic fever. The initial infection was characterized by discrete exudate on the pharynx. There was a moderate growth of type 14 streptococci on culture. The leukocyte count was 14,000. Penicillin therapy was started forty-eight hours after the first symptom. Clinically, this was a streptococcal infection although there was no immediate antibody response.

Twenty-two days after the onset of the sore throat a urticaria-like rash developed over the hands and feet which was associated with stiffness of the underlying joints. The maximum fever was 100.4°F. rectally and after the first day



there was no fever. There was a systolic murmur at the apex which did not vary while under observation. The sedimentation rate and leukocyte count were normal.

The clinical impression in this case was a penicillin reaction but because of fever, questionable arthralgia and skin rash possible rheumatic fever could not be excluded.

Patient P-2457 entered the hospital on April 15, 1949, giving a history of onset of sore throat at 6:00 A.M. Physical examination showed pin-head size exudate on the lymphoid tissue of the pharynx. The total leukocyte count was 12,300 and numerous streptococci of type 14 grew on culture of the throat. Treatment with penicillin was instituted nine hours after the onset of the infection. The initial antistreptolysin titer was 125 and twenty-six days later it was 625. Type 23 streptococci were present on the twenty-sixth day. On the fortieth day the antistreptolysin titer was 1,250 and a type 14 streptococcus was again isolated. The characteristics of the rheumatic fever episode, which began thirty-five days after the initial illness, are outlined in Table v.

In summary, acute rheumatic fever developed in this patient thirty-five days after a typical attack of acute streptococcal exudative pharyngitis. Penicillin therapy did not effectively inhibit antibody production. There is some evidence of an intervening infection as indicated by the new type of streptococcus isolated prior to the onset of rheumatic fever and by the continued increase of the antibody titer from 625 to 1,250. Other than the possibility of a second infection due to type 23 streptococcus there is no explanation for the failure of penicillin to prevent this complication.

Patient H-499 became ill March 3, 1949, with exudative pharyngitis. The leukocyte count was 23,500 and no streptococci were isolated on culture. Treatment with depot penicillin began thirteen hours after the onset of the illness. The antistreptolysin titer increased from <50 to 200 thirty-three days after the onset of the illness.

There was a history of acute rheumatic fever at the age of six and subsequently he was told that he had "leakage" of the heart.

Eighty-three days after the observed onset of exudative tonsillitis the symptoms of classic rheumatic fever began. (Table v.) On admission a history of sore throat, fever and chills two weeks before the onset of rheumatic symptoms was obtained. A type 14 streptococcus was

isolated and the antistreptolysin titer eighty-six days after the first attack of tonsillitis was 625.

To summarize, this patient probably had streptococcal exudative tonsillitis although the causative organism was not isolated. When he entered the hospital with acute rheumatic fever, he gave a history of an intervening streptococcal infection. It seems highly probable that the illness, eighty-three days before, for which he received penicillin was not the primary precipitating infection. The fact that there was an increase in the antibody titer from 200 to 625 confirms the history of a second streptococcal infection. In conclusion, this patient should probably not be classified as a penicillin failure since there is good evidence of a subsequent untreated streptococcal infection.

*Treatment According to Schedule II.* A total of 542 patients with exudative tonsillitis or pharyngitis were studied during the period that two doses of 300,000 units each of depot penicillin were employed. (Table I.) There were 254 patients who received penicillin on admission and again seventy-two hours later; 288 served as controls.

The distribution according to therapy of the thirteen cases classified as acute rheumatic fever and possible rheumatic fever, and ten patients with joint manifestations obtained by history, is shown in Table VI. Including both rheumatic fever categories there were ten cases in the control group and only three in the penicillin group. This is in contrast to the even distribution of patients with joint symptoms without other manifestations of rheumatic fever.

The details of each of the thirteen illnesses classified as rheumatic fever or possible rheumatic fever are presented in Table VII. This non-suppurative sequela developed six to 128 days following the onset of the observed attack of exudative tonsillitis or pharyngitis.

In this group of thirteen patients five showed bacteriologic evidence of an additional streptococcal infection between the observed exudative tonsillitis or pharyngitis and the rheumatic fever episode. One of these occurred in a group of seven cases in which the interval between the exudative tonsillitis and rheumatic fever was less than twenty-eight days, and the other four occurred in six patients in whom the interval was longer.

The observed attack of exudative tonsillitis or pharyngitis in these thirteen patients was streptococcal in origin in eight instances since there

TABLE V  
NON-SUPPURATIVE SEQUELAE DEVELOPING DURING STUDY OF PENICILLIN THERAPY, SCHEDULE I

Exudative Tonsillitis												Acute Rheumatic Fever												Remarks		
Case	Age	Treatment	WBC ÷ 1,000	Antistreptolysin "O"			Interval to Rheumatic Fever (days)	Admission		History		Physical Examination							Maxi- mum Tem- pera- ture	Laboratory						
				Acute Titer	Conva- lescent Titer	Tube In- crease		Throat Cul- ture	Cul- ture	ASL Titer	Fam- ily	Rheu- matic Fever	Heart Mur- mur	Joints						Rash	Heart	Sed. Rate 1,000	ECG			
														P	R	T	S	Mul.					Mig.		P-R (sec.)	Other
P 1657	18	0	15	100	200	3	A-NT	8	0	200	+	0	0	+	+	+	+	+	+	0	MS*	118	20	0.23	L 1, 2, 3, 4	Scarlet fever with tonsillitis
P 2377	20	0	..	250	1250	7	A-5	10	A-5	1250	0	0	0	+	0	0	+	0	0	Urti- caria	MS*	100	10	0.28	0	Developed otitis media 7 days after onset of tonsil- litis, received sulfadiazine
P 2639	19	0	..	159	625	6	A-5	11	A-5	625	+	+	0	+	+	+	+	+	0	MS*	103	17	0.23	0	.....	
P 1932	18	0	14	200	250	1	0	12	A-14	250	+	0	0	+	0	0	+	0	0	MS*	101	10	0.27	L 1, 4	Culture on second hospital day of first admission showed type 14 strepto- cocci	
H 557	21	0	13	125	500	6	A-14	14	A-14	500	0	+	+	+	0	+	+	+	0	MD	100	63	0.20	0	At age 10 had acute rheu- matic fever	
H 442	20	0	..	200	400	3	++	15	0	500	0	0	0	+	+	+	+	+	0	MS	104	115	0.16	0	90 days before rheumatic fever had streptococcal exudative tonsillitis due to group A, NT	
P 2668	17	0	15	50	250	7	A-24	17	A-24	250	0	0	+	+	+	+	+	+	0	MS*, TMD	104	92	0.44	0	One recurrence observed	
P 1931	19	0	35	125	625	7	A-5	17	A-5	625	0	+	..	+	+	+	+	+	0	MS*	104	96	0.21	0	.....	
H 612	23	0	13	159	400	4	A-14	19	A-14	400	+	0	0	+	0	0	+	+	0	0	101	83	0.24	0	65 days before rheumatic fever had streptococcal exudative tonsillitis due to group A, type 5; a type 1 streptococcus was isolated 29 days before rheumatic fever	
P 2640	27	0	13	125	500	6	A-5	22	0	500	0	0	0	+	+	+	+	+	Ery- thema margi- natum	MS*	104	107	0.28	0	Type 5 streptococcus iso- lated several times during course of rheumatic fever	
P 2802	20	0	13	<50	400	10	A-5	24	0	400	0	0	0	+	+	+	+	+	0	MS, TAD	105	125	0.16	0	.....	
P 1934	18	0	21	50	400	9	A-24	24	A-24	400	0	0	0	+	0	+	+	+	0	MS*	104	100	0.24	L 1, 4	.....	
P 3082	19	0	..	159	317	4	A-5	27	A-5	317	0	0	..	+	0	0	+	+	0	MS	100	35	0.27	0	Complained of abdominal pain	
H 554	19	0	20	83.3	317	6	A-NT	27	0	317	0	0	0	+	0	+	+	+	0	0	100	34	0.16	L 2, 3, 4	Classified as possible rheu- matic fever	
P 2198	20	0	16	<50	400	10	A-14	28	0	500	0	+	..	+	+	+	+	+	0	MS*	103	88	0.17	0	.....	
P 2461	23	0	12	400	400	0	A-14	29	A-14	400	0	+	0	+	+	+	+	+	0	MS*	103	96	0.20	0	See text	

H	338	19	0	9	.....	317	..	A-14	29	A-24	400	0	+	..	+	+	+	+	+	+	+	+	+	0	0	101	62	11	0.16	0	Classified as possible rheumatic fever; history and course of illness suggests rheumatoid arthritis
P	2460	20	0	14	125	400	10	A-14	30	A-14	400	0	0	0	+	+	+	+	+	+	+	+	0	0	104	77	10	0.32	L 1, 2		
P	2232	20	0	18	100	500	7	A-24	34	A-14	625	0	0	0	+	+	+	+	+	+	+	+	0	MS*	105	118	14	0.20	L 2, 3		
P	2366	18	0	..	250	500	3	A-24	38	A-5	500	+	0	0	+	+	+	+	+	+	+	+	0	MS	101	88	12	0.28	L 1	5 days before onset of rheumatic fever a type 14 was isolated; complained of a sore throat at this time	
P	1148	20	0	..	200	500	4	.....	38	0	500	0	0	0	+	+	+	+	+	+	+	+	0	MS*	102	104	14	0.20	0		
H	506	19	0	18	250	1250	7	A-5	43	A-NT	1250	0	0	0	+	+	+	+	+	+	+	+	Ery-thema multi-forme	Friction rub	105	112	21	0.20	0		
H	611	19	0	12	317	500	2	A-1	90	A-14	833	0	0	0	+	+	+	+	+	+	+	+	0	0	0	100	54	12	0.40	0	21 days before rheumatic fever had acute respiratory infection at which time streptococcus type 1 was isolated
R	19	20	0	..	125	200	2	A-24	110	A-5	250	+	0	0	+	+	+	+	+	+	+	+	0	MS*	101	47	10	0.24	0		
P	2311	18	Yes	10	159	200	1	0	221	A-5	250	0	+	+	+	+	+	+	+	+	+	+	0	MS*, AD ?MD	102	69	11	0.18	0		
P	2371	17	Yes	14	159	159	0	A-14	22	0	200	0	0	0	±	0	0	0	0	0	0	0	+	MS*	100.4	6	8	0.17	0	Had sore throat at onset of rheumatic fever with positive culture; may have acquired a new infection. Chorea and rheumatic fever at age 17; treated 4 days after onset of tonsillitis	
P	2467	20	Yes	12	125	625	7	A-14	35	A-14	1250	0	0	0	+	+	+	+	+	+	+	+	0	MS	102	101	12	0.16	0		
H	499	18	Yes	23	<50	200	7	0	83	A-14	625	0	+	+	+	+	+	+	+	+	+	+	0	MS	104	108	20	....	Complete heart block		

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Explanation: ASL: Antistreptolysin "O" titer

Family history: rheumatic fever or rheumatic heart disease

**Joints:** P = pain, R = redness, T = tenderness, S = swelling, Mul. = multiple involvement of joints, Mig. = migrating involvement of joints

**Heart:** MS = mitral systolic murmur, MD = mitral diastolic, AS = aortic systolic, AD = aortic diastolic, \* = murmur considered significant (see Table II)

Sed. rate: Maximum sedimentation rate (Westergren)

ECG: Maximum P-R interval recorded

L indicates inversion of T wave



was an immediate rise in the antistreptolysin titer. There were four cases (P-1295, P-1261, P-1922 and H-589) in which the serologic tests were not diagnostic of a streptococcal infection and one patient (P-2596)\* from whom no con-

TABLE VI  
NON-SUPPURATIVE SEQUELAE DEVELOPING IN 542 PATIENTS  
OBSERVED DURING PENICILLIN THERAPY, SCHEDULE II

Classification	No. of Patients	
	Treated (254)	Control (288)
Definite rheumatic fever . . . . .	2	6
Possible rheumatic fever . . . . .	1	4
Others*		
Joint pains . . . . .	4	4
Joint pains and swelling . . . . .	1	..
Joint pains and feverishness . . . . .	..	1
Totals . . . . .	8	15

\* Exclusive of first two diagnostic categories

valescent blood was available. The details of these illnesses follow:

Patient P-1295 showed a small amount of exudate on the tonsils, the leukocyte count was 11,500 and the throat culture showed a predominant growth of type 5 streptococci. In eighteen days numerous type 5 streptococci were still isolated on culture and the titer of antistreptolysin had increased from 159 to 200; by the thirty-fourth day, however, the antistreptolysin titer was 250. These data indicate that the illness was caused by type 5 streptococci.

Case P-1261 had an initial antistreptolysin titer of 625. Fifteen days and twenty-four days from onset the titer was still 625. Type 14 streptococci were isolated on admission, and the leukocyte count was 15,200. The failure to show a rise in the antistreptolysin titer may have been due to the fact that the initial titer was elevated.

The illness in Case P-1922 began on February 20, 1949, and did not appear to be due to the streptococcus. Examination showed pinhead size exudate on the tonsils; the cervical lymph nodes were not enlarged or tender. Rales were present over the right lower lung. No streptococci were isolated on culture and the antistreptolysin titer fell from 250 to 159 thirty-two days after the onset. Symptoms of rheumatic fever began forty-three days after the onset of

tonsillitis and three days later the antibody titer was 250. On the fifty-eighth day a type 24 streptococcus was isolated. It seems probable that the observed illness was non-streptococcal and that prior to the onset of rheumatic fever the patient had an intervening streptococcal infection which failed to produce a recognizable illness.

In patient H-589 an illness characterized by discrete exudate on the tonsils and tender and enlarged cervical lymph nodes was observed 128 days before the onset of rheumatic fever. The leukocyte count was 19,700; and although streptococci were not isolated, the antistreptolysin titer increased from 317 to 400 by the thirty-fifth day. On the same day a non-typeable group A streptococcus was isolated. Twenty-three days after the onset of exudative tonsillitis he was readmitted with an acute respiratory infection without exudative tonsillitis or pharyngitis. Numerous type 5 streptococci were isolated from the culture at this time and the leukocyte count was 14,000. By the fifty-sixth day from the original illness the antistreptolysin titer was 500. These data indicate that one, if not both, of these illnesses was caused by the streptococcus. In addition, one week after admission for acute rheumatic fever a type 14 streptococcus was identified in several cultures and the antistreptolysin titer became 833. It appears likely that the patient had experienced another streptococcal infection at about the time acute rheumatic fever developed.

There were three patients in whom a non-suppurative sequela developed after having received two injections of penicillin.

In patient P-1930 a disease classified as possible rheumatic fever developed twenty-five days after the onset of a type 24 streptococcal infection complicated by peritonsillar cellulitis. (Table VII.) This patient had an odd serial number and was given depot penicillin in the prescribed dosage 106 hours after the onset at the request of the ward physician. Since only depot penicillin was administered, this case was not excluded from the study. Streptococci were eradicated from the oropharynx but penicillin apparently did not prevent the formation of antibody.

Patient P-2596 had a questionable streptococcal illness sixty-eight days before the onset of rheumatic fever. There was pinhead size exudate on the pharynx, the cervical lymph nodes were tender but not enlarged and the leukocyte count was 9,600. Streptococci were not isolated

\* Discussed under penicillin failures.



TABLE VII  
 NON-SUPPURATIVE SEQUELAE DEVELOPING DURING STUDY OF PENICILLIN THERAPY, SCHEDULE II

Exudative Tonsillitis										Acute Rheumatic Fever										Remarks						
Case	Age	Treat- ment	WBC ÷ 1,000	Antistreptolysin "O"			Throat Cul- ture	Inter- val to Rheu- matic Fever (days)	Admission		History		Physical Examination						Maxi- mum Tem- pera- ture		Laboratory					
				Acute Titer	Conva- lescent Titer	Tube In- crease			Cul- ture	ASL Titer	Fam- ily	Rheu- matic Fever	Heart Mur- mur	Joints							Rash	Heart	Sed. Rate ÷ 1,000	ECG		
														P	R	T	S	Mul.						Mig.	P-R (sec.)	Other
H 92	19	0	10	100	833	9	A-24	6	A-5	833	0	0	0	0	0	0	0	0	0	0	103	92	13	0.28	0	23 days after onset of rheu- matic fever, ASL titer was 250
P 1295	20	0	11	159	200	1	A-5	11	A-5	200	0	+	0	+	0	0	0	0	0	0	103	60	11	0.44	0	
P 1261	19	0	15	625	625	0	A-14	14	A-14	625	0	±	0	+	0	0	0	0	0	0	100.4	39	11	0.16	0	
P 1507	18	0	16	125	317	4	A-6	15	A-6	317	+	0	0	+	+	0	0	0	0	0	101	16	9	0.15	0	
P 1577	17	0	28	159	625	6	A-5	22	0	625	0	0	0	0	0	0	0	0	0	0	101	44	10	0.20	0	P-R interval decreased to 0.14 sec. Possible rheu- matic fever
P 1263	19	0	16	250	500	3	A-14	26	A-14	500	0	0	0	0	+	+	0	0	0	0	101	50	..	0.14	0	Possible rheumatic fever
P 1188	18	0	18	62.5	200	5	A-24	28	0	250	0	0	0	0	+	+	+	+	+	+	101	22	14	0.30	0	4 days prior to onset of rheumatic fever, developed respiratory infection; type 5 was isolated at this time
P 1922	20	0	..	250	159	-2	0	43	C	250	+	0	0	0	+	+	+	+	+	+	101	66	10	0.17	0	11 days before onset of rheu- matic fever, culture nega- tive; a type 24 isolated 14 days after onset of rheu- matic fever
P 1927	18	0	15	62.5	1000	12	A-5	64	A-14	1250	+	0	0	0	+	+	+	+	+	+	103	126	15	0.28	0	35 days before onset of rheumatic fever, had A-5 in throat culture
H 589	19	0	19	317	400	1	0	128	0	500	0	0	0	0	+	+	+	+	+	+	104	114	15	0.24	0	See text; evidence of sev- eral streptococcal infec- tions
P 1930	38	Yes	15	<50	200	7	A-24	25	0	200	0	0	0	0	+	0	0	0	0	0	101	16	9	0.15	0	Patient had odd serial num- ber, treated 106 hr. after onset at request of ward physician because of peri- tonsillar cellulitis. Possible rheumatic fever
P 2596	19	Yes	9	100	....	...	0	68	A-23	500	+	0	0	0	+	+	+	+	+	+	100	20	12	0.23	0	Treated 3 days after onset of exudative pharyngitis
P 2711	19	Yes	11	125	200	2	A-5	100	0	625	0	0	0	0	+	+	+	+	+	+	102	84	13	0.17	0	Treated 34 hr. after onset; history of infection 2 wk. before rheumatic fever and a non-typable strain iso- lated shortly after admis- sion; serologic confirma- tion of new infection

See footnote Table v for explanations.

from the cultures of the throat. Treatment of this questionable case of streptococcal exudative pharyngitis was instituted 3 days after the onset of the illness. No convalescent blood was obtained but at the time of admission for rheumatic fever a type 23 streptococcus was isolated and the antibody titer was elevated.

TABLE VIII  
NON-SUPPURATIVE SEQUELAE DEVELOPING IN 582  
PATIENTS OBSERVED DURING PENICILLIN THERAPY,  
SCHEDULE III

Classification	No. of Patients	
	Treated (290)	Control (292)
Definite rheumatic fever . . . . .	2	7
Possible rheumatic fever . . . . .	1	1
Others *		
Joint pains . . . . .	8	3
Joint pains and swelling . . . . .	1	2
Joint pains and feverishness . . . . .	1	2
Joint pains, swelling and feverishness . . . . .	1	
Totals . . . . .	14	15

\* Exclusive of the first two categories.

In case P-2711 a typical streptococcal infection developed 100 days before the first symptom of rheumatic fever. The infection was caused by type 5 streptococci. Treatment was instituted thirty-four hours after the onset of the disease and cultures taken four and eleven days later showed no streptococci. The convalescent antistreptolysin titer measured on blood taken eleven days after onset was 200, compared to an initial titer of 125, which established the streptococcal etiology of this infection. At the time of onset of the rheumatic fever the antibody titer was 625 and a non-typeable group A streptococcus was isolated subsequently. With a history of a respiratory infection two weeks before the attack of rheumatic fever, it appears highly probable that the observed infection characterized by exudate and treated with penicillin was not the primary initiating infection.

In summary, then, the two patients with definite rheumatic fever probably had an intervening streptococcal infection and therefore may not necessarily represent true penicillin failures. Patient P-1930 was treated late in the course of the illness because of a complication and subsequently possible rheumatic fever

developed. In this case late treatment may have been responsible for the failure.

*Treatment According to Schedule III.* The prophylactic effect of a single injection of 600,000 units of depot penicillin was studied in 290 patients with exudative tonsillitis or pharyngitis while 292 patients served as controls. (Table I.) There were eleven patients in whom a non-suppurative sequela developed and eighteen who complained of joint symptoms without other signs of rheumatic fever during the several weeks following the streptococcal infection. The distribution of these cases between the treated and control groups is presented in Table VIII.

There were seven instances of acute rheumatic fever in the control group and two in the treated group, a difference that is probably not due to chance alone. The number of patients with joint symptoms is greater in the treated than in the control group.

The details of the illnesses in patients in whom rheumatic fever subsequently developed are presented in Table IX. In this group of eleven patients acute rheumatic fever developed seventeen to 171 days following the observed attack of exudative tonsillitis or pharyngitis. There was a total of five patients who had definite bacteriologic evidence of two infections by different types of streptococci, all among the eight patients in whom the interval was over thirty-three days. In addition, in patients R-67 and R-48 there was a history of an intervening streptococcal infection before the onset of rheumatic fever.

The antistreptolysin titers on the acute and convalescent sera establish the streptococcal etiology of all but four (R-36, R-63, R-67 and R-48\*) of the observed attacks of exudative tonsillitis or pharyngitis in this group of eleven patients. (Table IX.)

Patient R-36 had discrete exudate on the pharynx, tender cervical lymph nodes and numerous type 14 streptococci on culture of the throat. The leukocyte count was 14,000. There was only a one dilution increase in antistreptolysin but it appears highly probable that this infection was streptococcal in origin.

Case R-63 had enlarged, tender cervical lymph nodes and discrete exudate on the tonsils. There were numerous type 28 streptococci on culture and the leukocyte count was 6,000. The antistreptolysin titer increased slightly from 62.5 on admission to 83.3 four weeks later. It is

\* Discussed under penicillin failures.

TABLE IX  
 NON-SUPPURATIVE SEQUELAE DEVELOPING DURING STUDY OF PENICILLIN THERAPY, SCHEDULE III

Exudative Tonsillitis				Acute Rheumatic Fever										Remarks																		
Case	Age	Treatment	WBC ÷ 1,000	Antistreptolysin "O"			Interval to Rheumatic Fever (days)	Admission		History		Physical Examination						Laboratory														
				Acute Titer	Conva- lescent Titer	Throat Cul- ture		Cul- ture	ASL Titer	Rheu- matic Fever	Heart Mur- mur	Joints						Rash	Heart	Maxi- mum Tem- pera- ture	Sed. Rate	WBC ÷ 1,000	P-R (sec.)	ECG								
												P	R	T	S	Mul.	Mig.															
R 46	20	0	..	62.5	400	8	A-14	17	A-14	317	0	0	+	+	+	+	+	+	Ery- thema margi- natum	MS* AD	MS*	104	104	12	0.32	J <sup>1</sup>	Had exudative tonsillitis at time of onset of rheumatic fever					
R 26	18	0	15	100	400	6	A-5	17	A-5	250	0	0	+	+	+	+	+	+	0	Friction rub MS*	Friction rub MS*	105	109	11	0.28	J <sup>4</sup>						
R 51	19	0	..	83.3	400	7	A-14	19	A-14	400	0	0	+	+	+	+	+	+	0	Friction rub MS*	Friction rub MS*	100	92	14	0.21	0						
R 36	21	0	14	125	159	1	A-14	35	A-NT	159	0	0	+	+	+	+	+	+	0	MS	MS	103	60	14	0.23	0						
R 59	20	0	..	125	500	6	A-14	45	A-24	625	0	0	+	+	0	0	+	+	0	0	0	99	36	8	0.16	0						Possible rheumatic fever
R 63	19	0	6	62.5	83.3	1	A-28	60	A-14	625	0	0	+	+	+	+	+	+	0	MS	MS	101	78	12	0.20	0						Negative culture 29 days after onset of tonsillitis; 19 days before rheumatic fever had exudative tonsil- litis with 33,000 WBC, and type 14 streptococci. Re- ceived no treatment
R 49	19	0	15	159	317	3	A-24	85	0	317	0	0	+	+	+	+	+	+	Pur- pura	MS*	MS*	105	106	14	0.20	0						28 days after onset of rheu- matic fever, type 14 be- lained and antistreptolysin was 625; had exudative tonsillitis on admission for rheumatic fever
R 67	18	0	11	100	100	0	0	171	A-14	500	0	0	+	+	0	0	+	+	0	0	0	100	102	12	0.40	0						History of sore throat 1 mo. before onset of rheumatic fever
R 73	20	Yes	..	100	159	2	A-14	34	A-5	250	0	0	+	+	0	0	+	+	0	MS	MS	100	74	7	0.20	0						Possible rheumatic fever; treated 72 hr. after onset of exudative pharyngitis
R 37	22	Yes	10	62.5	100	2	A-24	52	A-24	250	0	0	+	+	+	+	+	+	0	0	0	101	50	10	0.20	0						Treated 9 hr. after onset of exudative pharyngitis. His- torical and serologic evi- dence of intervening infec- tion
R 48	19	Yes	7	62.5	62.5	0	0	72	A-14	400	0	0	+	+	0	+	+	+	0	MS*	MS*	102	76	10	0.37	0						20 days before onset of rheu- matic fever, had another attack of tonsillitis caused by type 14 streptococci; ASL response of 8 tubes; received no treatment

See footnote Table v for explanations.



somewhat doubtful whether this illness was a streptococcal infection. Nineteen days before the onset of rheumatic fever and after this study was completed, a typical streptococcal illness was observed caused by type 14 streptococci. This illness was not treated. There was an immediate increase in antibody and rheumatic fever developed sixty days after the original infection observed during the study of schedule III. It appears highly probable that the acute attack of tonsillitis nineteen days before the onset of rheumatic fever was the precipitating illness.

Case R-67 had discrete exudate on the tonsil with peritonsillar cellulitis. The lymph nodes were enlarged and tender; the leukocyte count was 11,000 but no streptococci were isolated on culture. Whether this illness was streptococcal or not cannot be determined. Acute rheumatic fever developed 171 days later; the patient gave a history of a sore throat one month previously; a type 14 streptococcus was isolated and the antistreptolysin titer increased markedly. It is definite that this patient had an intervening streptococcal infection.

There were three patients who received a single injection of penicillin and subsequently possible or definite rheumatic fever developed thirty-four to seventy-two days later. The details of these illnesses are presented below.

Patient R-73 became ill on February 3, 1950. On examination discrete exudate was found on the pharyngeal lymphoid tissue and the cervical lymph nodes were enlarged and tender. Cultures showed a predominant growth of type 14 streptococci. A single injection of 600,000 units of penicillin was given seventy-two hours after onset. Twenty-five days after onset the culture showed no streptococci and the antistreptolysin titer was 159 compared to a titer of 100 on admission to the hospital. On the thirty-fourth day the left knee became painful on motion. The next day the pain was gone but now the left shoulder and a day later the right shoulder became painful for a day. There were no other symptoms. On the thirty-ninth day he was hospitalized and numerous type 5 streptococci were isolated.

During a two-week period of observation the rectal temperatures were normal and no further symptoms developed. The electrocardiograms were normal and the maximum sedimentation rate was 74. The antistreptolysin titer was now 250.

This patient probably had a type 14 streptococcal exudative pharyngitis for which he received penicillin. A cross infection with type 5 streptococci occurred and may have been responsible for the development of the post-streptococcal reaction which was of minor degree.

Patient R-37 had a sore throat on December 2, 1949. Small areas of exudate were observed on the pharyngeal tissues and the lymph nodes were not enlarged or tender. The total leukocyte count was 10,000. Numerous type 24 streptococci were isolated from the throat culture. A single injection of penicillin was given nine hours after the onset of the illness. The acute phase serum and a serum taken on the thirty-third day showed 62.5 and 100 units of antistreptolysin, respectively.

During the fifty-two-day interval between the observed illness and acute rheumatic fever, he had two attacks of severe sore throat for which he reported to the dispensary for therapy. Fifty-four days after the original infection type 24 streptococci were again isolated and the antistreptolysin titer was now 250. Signs of active rheumatic fever were present for nine weeks. (Table IX.)

In summary this patient was treated nine hours after the onset of an attack of exudative pharyngitis. Although the clinical features were not those usually observed in streptococcal sore throat, there was a diagnostic increase in the antistreptolysin titer thirty-four days later. Because of the long interval between the attack of pharyngitis and rheumatic fever and since there was historical evidence of new infections, it was thought that this patient had an intervening streptococcal infection. The increase in antistreptolysin from 100 to 250 confirms this impression but a new type of streptococcus was not isolated. It is entirely possible that penicillin treatment inhibited type-specific antibodies sufficiently so that immunity was not acquired and that this patient acquired a second infection due to the same type of streptococcus causing the original disease.

Patient R-48 entered the hospital on December 23, 1949, stating that he had developed a sore throat twenty-four hours previously. There was discrete exudate on the tonsils with little associated redness of the surrounding tissues. The cervical lymph nodes were not tender. Treatment was administered twenty-three hours after onset. The antistreptolysin titers were 62.5



on admission and again thirty-five days after onset. Throat cultures on admission and at follow-up showed no beta-hemolytic streptococci.

On February 12th he again developed a sore throat with discrete exudate over the tonsils. With this illness, however, the lymph nodes

In summary the initial attack of acute tonsillitis for which he received penicillin was probably an example of non-streptococcal exudative tonsillitis.<sup>11</sup> The second attack twenty days prior to the onset of rheumatic fever was undoubtedly streptococcal in origin. Therapy with penicillin

TABLE X  
EFFECT OF THREE DIFFERENT SCHEDULES OF PENICILLIN ON GROUP A STREPTOCOCCI

Time of Cultures	Penicillin Schedule											
	I				II				III			
	Treated		Control		Treated		Control		Treated		Control	
	No. Cultured	Positive (%)	No. Cultured	Positive (%)	No. Cultured	Positive (%)	No. Cultured	Positive (%)	No. Cultured	Positive (%)	No. Cultured	Positive (%)
Group A on admission . . .	626	78.4	571	85.6	251	66.5	287	66.9	290	70.7	292	71.6
Group A on follow-up examination . . . . .	508	12.8	482	51.9	200	17.5	234	44.0	257	30.7	269	56.5

TABLE XI  
EFFECT OF THREE DIFFERENT PENICILLIN SCHEDULES ON THE INFECTING TYPE OF BETA-HEMOLYTIC STREPTOCOCCUS

	Penicillin Schedule											
	I				II				III			
	Treated		Control		Treated		Control		Treated		Control	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Typeable group A streptococci on admission . . . . .	426	...	422	....	156	...	173	....	178	....	183	....
Same type at follow-up . . . . .	29	6.8	146	34.6	12	7.7	51	29.5	51	28.7	110	60.0
New type at follow-up . . . . .	19	4.5	28	6.6	13	8.3	18	10.4	4	2.2	8	4.4

were enlarged and tender, the leukocyte count was elevated to 12,000 and the throat cultures showed a profuse growth of type 14 streptococci. The antistreptolysin titer was still 62.5 but increased to 400 twenty-three days later. Acute rheumatic fever began seventy-two days after the initial illness and twenty days after the second illness.

was not administered at this time because he was included in another study. It is clear, then, that this instance of rheumatic fever cannot be ascribed to the failure of penicillin.

*Effect of Penicillin on Group A Streptococci.* The effects of the various dosage schedules of penicillin used in this study on group A streptococci are summarized in Tables x and xi. In Table x

the group A carrier rates at time of hospitalization and at the time of the follow-up examination are presented.

As mentioned previously, the group A carrier rate at time of hospitalization varied from 66.5 to 85.6 per cent which was due to the inclusion of varying numbers of patients with non-streptococcal exudative tonsillitis. Likewise, at the time of re-examination the carrier rates of group A streptococci in the control groups varied. There are numerous factors which may be responsible for this variation such as the opportunity to acquire new types of streptococci and differences in the times that the cultures were obtained. During schedule III, for example, approximately 25 per cent of the cultures were taken before the twenty-eighth day, whereas in schedules I and II only 14 and 12 per cent, respectively, of the cultures were taken by this time.

In spite of the variation in the carrier rates during the course of the study it is apparent from the data presented in Table X that penicillin therapy resulted in a reduction of group A streptococci when compared to the results obtained in control groups. Furthermore, there was a definite relationship between the effectiveness of such treatment and the dosage schedule of penicillin. The carrier rates were decreased most by the penicillin dosage schedule I and least by schedule III.

In order to determine more specifically the effect of penicillin on the infecting organism an analysis was made of the cultures from all individuals found to harbor a typeable strain on admission to the hospital. If this strain was still present at the time of follow-up examination, it is reasonable to assume that the individual harbored the organism throughout the period between the two positive cultures.\* A change of type between the two cultures would then indicate the acquisition of a new organism. The analysis of the effect of therapy on the streptococcus responsible for the infection as well as the effect on new acquisitions is presented in Table XI.

The convalescent carrier rates for the infecting type in the control groups of schedules I, II and III were 34.6, 29.5 and 60 per cent, respectively. The explanation for the high convalescent carrier rate in the untreated patients in the

third group is not known but it may be due in part to the fact that cultures were taken at an earlier date than during the other two schedule periods. Although the type distribution was different in schedule III compared to schedules I and II, no evidence was found to indicate that the convalescent carrier rate is a function of the serologic type of streptococcus.

The data in Table XI establish that penicillin treatment effects a reduction of both the infecting strain of streptococcus as well as new types of organisms. The per cent reduction in the carrier rates for the specific infecting serologic type of streptococcus by therapy with depot penicillin was greatest in schedule I and least in schedule III. The reduction in the group A carrier rates was due primarily to eradication of the infecting type.

Although the number of airmen who acquired a new organism was not great, from 4.4 to 10.4 per cent of the control groups were known to harbor a new type. In each instance there was a reduction in the number acquiring a new type in the treated groups as compared to the controls. This reduction may have resulted from the protection afforded by antibiotic therapy against cross infections in the hospital.

Since penicillin therapy prevented the subsequent occurrence of rheumatic fever, the data were reviewed to determine whether this was related to the eradication of the streptococcus from the oropharynx. Of those rheumatic subjects who harbored streptococci on admission for the observed attack of exudative tonsillitis or pharyngitis and received no treatment, 66 per cent still harbored a group A streptococcus at the time of follow-up examination, whereas 51 per cent of all the control patients in whom rheumatic fever failed to develop still carried a group A streptococcus. In the treated patients who had group A streptococci on admission for the observed respiratory infection and who subsequently developed definite or possible rheumatic fever, one of seven still harbored group A streptococci at the time of follow-up examination. These results fail to show any relationship of the carrier state to the development of rheumatic fever.

*Effect of Therapy on Antistreptolysin Production.* The acute and convalescent titers of antistreptolysin in the treated and control groups are presented in Figures 1, 2 and 3. These data are presented in detail since the ability to demonstrate an increase in the antibody titer following

\* In a few instances there may have been a reacquisition of the same organism.



a streptococcal infection is related to the initial titer.<sup>12</sup>

Inspection of the data in Figures 1, 2 and 3 shows that penicillin therapy did result in the inhibition of antistreptolysin. In each series the distribution of the initial antistreptolysin titers

inhibition. Analyses showed that more patients with infections not due to group A streptococci were included in the groups entering the hospital three and four days after the onset of the illness than during the first forty-eight hours. For example, 23 per cent of the admission cultures

		CONVALESCENT ANTISTREPTOLYSIN TITER														TOTALS
		<50	50	62	83	100	125	159	200	250	317	400	500	625	833	
ACUTE ANTISTREPTOLYSIN TITER	833	PENICILLIN														1
	625	300,000 UNITS STAT														2
	500	300,000 UNITS 48 hrs.														4
	400	600,000 UNITS 96 hrs.														3
	317		1	1	2		3	5	1	4						18
	250					1	12	6								29
	200					2	7	14	10	5						40
	159					1	3	15	24	10	4					64
	125					1	3	19	26	19	5	4				81
	100					2	1	12	27	15	8	7	2			79
	83						7	10	11	5	3					40
	62						6	10	18	17	3					62
	50						3	1	3	1	2	6	2	3		25
	<50						10	8	13	4	11	6	4	2	1	60
TOTALS		13	9	25	26	57	86	78	69	56	39	26	13	4	2	508
ACUTE ANTISTREPTOLYSIN TITER	625	CONTROL														4
	500															7
	400															7
	317															8
	250															26
	200															34
	159															56
	125															73
	100															68
	83															51
	62															64
	50															29
	<50															46
TOTALS		3	3	8	9	24	48	54	64	72	47	49	37	27	9	473

FIG. 1. Effect of penicillin therapy (schedule i) on antibody formation. Figures refer to number of cases; area within diagonal lines represents changes considered not significant.

is approximately the same. Since the number of true streptococcal infections varied somewhat during the study, the degree of inhibition of antibody by penicillin is best expressed as the per cent reduction in the antibody increase as compared to the untreated patients in the same schedule. The degree of inhibition produced by penicillin in schedule i was 51 per cent, in schedule ii, 38 per cent and in schedule iii, 26 per cent. It is apparent from these figures then that insofar as the suppression of antibody is concerned the use of three injections totaling 1,200,000 units of depot penicillin was twice as effective as a single injection of 600,000 units.

Since penicillin treatment inhibited antibody formation, the data were examined to determine the effect of time of treatment on the degree of

		CONVALESCENT ANTISTREPTOLYSIN TITER														TOTALS
		<50	50	62	83	100	125	159	200	250	317	400	500	625	833	
ACUTE ANTISTREPTOLYSIN TITER	500	PENICILLIN														1
	400	300,000 UNITS STAT														1
	317	300,000 UNITS 72 hrs.														1
	250															9
	200															19
	159															16
	125															33
	100															32
	83															7
	62															33
	50															14
	<50															32
TOTALS		11	1	16	19	21	28	29	25	19	14	7	5	2	1	198
ACUTE ANTISTREPTOLYSIN TITER	625	CONTROL														2
	500															4
	400															4
	317															10
	250															12
	200															11
	159															32
	125															31
	100															32
	83															26
	62															34
	50															17
	<50															15
TOTALS		1	6	9	8	12	17	30	30	31	30	15	17	14	5	230

FIG. 2. Effect of penicillin therapy (schedule ii) on antibody formation. (See Figure 1.)

were negative for beta-hemolytic streptococci from patients treated between twenty-four and forty-seven hours after the onset of illness in schedule i whereas in those patients ill for forty-eight to seventy-one hours before treatment was started, 42 per cent had negative cultures. The analyses to be presented, therefore, were limited to individuals who showed group A streptococci on the admission culture. A few patients who were merely carriers of streptococci and who had non-streptococcal tonsillitis are undoubtedly included and are most likely in the groups of patients entering the hospital after the second day of illness. The average increment change in titer of antistreptolysin in this group is presented in Table xii.



The data again demonstrate that in those patients treated within twenty-four hours of the onset of the illness, schedule I is more effective than schedules II and III in inhibiting antibody formation. Furthermore, there is a slight tendency for delay in therapy to result in less inhibi-

that cultures of the throat and antistreptolysin titers on acute and convalescent phase sera were obtained to confirm the streptococcal etiology of the observed illnesses. These studies established the fact that the majority of the infections in treatment schedule I were caused by group A

		CONVALESCENT ANTISTREPTOLYSIN TITER															TOTALS	
		<50	50	62	83	100	125	159	200	250	317	400	500	625	833	1000		1250
ACUTE ANTISTREPTOLYSIN TITER	400	PENICILLIN																
	317	600,000 UNITS STAT															2	
	250									3	2	1						6
	200								1	9	7		1					18
	159							1	5	9	4	1	6	1				27
	125							3	9	8	7	5	2			2		36
	100						3	15	4	4	10	4	3		1	1		45
	83			1		1	9	5	8	4	1	2	1		1	1		34
	62			1	2	4	6	5	4	1	1			1	1			26
	50		2	7	7	8	2	4	2	2	1	1		2				38
	<50		3	2	1	2	2		1	2								13
TOTALS	4	4	1			1		1		2				1	1	1	16	
		4	9	12	11	27	33	32	29	43	27	11	8	8	6		1	261
ACUTE ANTISTREPTOLYSIN TITER	833	CONTROL															1	
	625																	1
	500																	
	400																	
	317												2	2				4
	250											1	2	4	1			8
	200											1	1	2	3	2	1	10
	159																	
	125																	
	100																	
	83																	
	62																	
	50																	
	<50																	
TOTALS	7	8	13	14	19	30	33	17	33	25	29	24	9	5	1	1	1	269

FIG. 3. Effect of penicillin therapy (schedule III) on antibody formation. (See Figure 1.)

tion of antibody than when penicillin is given early in the course of the illness. This is best shown by the average dilution increase during schedule III and less so during schedule II. In schedule I there was apparently more inhibition of antibody in patients treated forty-eight to seventy-one hours after the onset than in those treated earlier. The explanation for this observation is not apparent.

#### COMMENTS

For the purposes of this study a rapid method of selection of patients with streptococcal disease was required. Since exudate on the tonsils or oropharynx is observed in 70 to 90 per cent of patients admitted to army hospitals with streptococcal tonsillitis or pharyngitis,<sup>13-15</sup> this single criterion was used in the selection of cases for study. Exudative lesions of the oropharynx are also associated with other respiratory diseases so

TABLE XII

EFFECT OF THE INTERVAL BETWEEN THE ONSET OF INFECTION AND THE TIME OF TREATMENT ON THE INHIBITION OF ANTISTREPTOLYSIN\*

Treatment Schedule		Interval in Hours Between Onset of Illness and Treatment		
		0-23	24-47	48-71
I	No. of observations	103	186	90
	Average dilution increment change in antibody	2.00	2.04	1.79
II	No. of observations	38	65	25
	Average dilution increment change in antibody	2.21	2.03	2.56
III	No. of observations	48	84	38
	Average dilution increment change in antibody	2.38	2.77	3.66

\* Includes only those patients whose initial throat culture showed group A streptococci.

streptococci. While treatment schedules II and III were being used, a number of patients with non-streptococcal exudative tonsillitis and pharyngitis<sup>11</sup> were included in the study groups. In concurrence with observations of others<sup>15,16</sup> these non-streptococcal exudative infections were observed at the same time that outbreaks of acute undifferentiated respiratory diseases were occurring.

The variation in the number of group A streptococcal infections observed during the course of these studies is reflected also in the incidence of rheumatic fever. Thus rheumatic fever and possible rheumatic fever occurred in 4.93, 4.18 and 2.96 per cent of the untreated patients followed for at least three weeks after the observed infection during the study of treatment schedules I, II and III, respectively.

That the treatment of streptococcal infections with penicillin results in a decreased incidence of acute rheumatic fever is established by the

distribution of cases between the control and treated patients. There was a total of forty-two patients in the control groups and only ten patients in the treated groups who developed rheumatic fever or possible rheumatic fever following the observed illness.

A detailed analysis of the collected data on rheumatic subjects in both the treated and untreated groups was made in an attempt to explain the failure of penicillin to prevent rheumatic fever in all cases. It was found that when the time interval between the onset of exudative tonsillitis or pharyngitis and the onset of rheumatic fever was prolonged, there was bacteriologic, serologic or historical evidence of an intervening untreated streptococcal infection in many instances. This is in contrast to the almost complete lack of such evidence of a second infection in those patients where the interval was short. The average interval between the two illnesses was fifty-one days in the ten treated patients and thirty-six days in the forty-two control patients. In five of the ten cases of rheumatic fever or possible rheumatic fever in the treated groups the interval was over forty-five days whereas in only seven of forty-two cases in the control group was the interval this long. These data indicate that penicillin therapy of acute streptococcal infections exerts little effect on rheumatic fever developing after a long latent period.

In view of the fact that penicillin therapy could not be expected to prevent rheumatic fever when an intervening streptococcal infection is not treated with the drug, all patients in whom this sequela developed after forty-five days from the onset of the observed illness are excluded for the purpose of discussion. In Table XIII the distribution of cases of definite and possible rheumatic fever between the treated and control groups is presented. There were a total of 978 treated patients who remained at the Air Base at least until the time of the follow-up examination and only two developed definite rheumatic fever. This is in contrast to twenty-eight patients with rheumatic fever in the control group of 996 patients who were known to reside at this Air Force Base for at least three or more weeks. The difference between the incidence of rheumatic fever in the treated and control groups is highly significant. The attack rate was reduced from 2.81 per cent in the controls to 0.2 per cent in the treated patients.

Examination of the data (Table XIII) shows

that during the period when three injections of penicillin were administered (schedule I) the incidence of rheumatic fever was definitely decreased by treatment. This was true not only for the disease readily recognized as rheumatic fever but penicillin also decreased the incidence

TABLE XIII  
POST-STREPTOCOCCAL SEQUELAE DEVELOPING WITHIN  
FORTY-FIVE DAYS AFTER AN ATTACK OF EXUDATIVE  
TONSILLITIS OR PHARYNGITIS

Treatment Schedule	Classification	No. of Patients		P Value
		Treated	Control	
I	No. of patients*	516	487	.....
	Definite rheumatic fever	2	20	<0.001
	Possible rheumatic fever	1	2	.....
II	No. of patients*	200	239	.....
	Definite rheumatic fever	0	4	0.129
	Possible rheumatic fever	1	4	.....
III	No. of patients*	262	270	.....
	Definite rheumatic fever	0	4	0.124
	Possible rheumatic fever	1	1	.....
Totals	No. of patients*	978	996	.....
	Definite rheumatic fever	2	28	<0.001
	Possible rheumatic fever	3	7	.....

\* Includes only patients who had a follow-up examination.

of joint pains without other evidence of rheumatic fever. These observations indicate that perhaps the pathogenesis of post-streptococcal arthralgia is similar to acute rheumatic fever and varies only in degree.

Since the number of patients studied during schedules II and III was relatively few, it is impossible to conclude with certainty that either two injections of 300,000 units of depot penicillin given seventy-two hours apart or a single injection of 600,000 units is as effective in preventing rheumatic fever as the larger dose (schedule I). There were four instances of acute rheumatic fever in each of the control groups of treatment schedules II and III and no cases in the treated groups. (Table XIII.) These differences may have occurred by chance twelve times in 100 observations; but if the two series are combined, this distribution of cases would have occurred only eight times in 1,000 observations. It would appear, therefore, that on the basis of this evidence alone, a single injection of 600,000 units or two injections of 300,000 units of depot penicillin is effective in decreasing the incidence of rheumatic fever.

In contrast to the decreased incidence of joint



pains in the absence of other objective criteria of rheumatic fever in the patients treated with three injections of penicillin, there was no decrease in the incidence of these complaints in the treated patients during the study of penicillin schedules II and III. This may be due to the possibility that penicillin in the dosage used in schedules II and III was not maximally effective.

There is little doubt that penicillin in the dosage used eradicated the group A streptococcus from the throat in many instances and also inhibited antibody formation. There was a definite correlation between elimination of the carrier state and the penicillin dosage schedule used. The data indicate that the duration of treatment is an important factor in this regard. Thus a total of 600,000 units given in two injections seventy-two hours apart was more effective in the eradication of streptococci than a single injection of 600,000 units. Furthermore, during treatment according to schedule I, the carrier state was decreased to a greater degree than by penicillin administered according to either schedule II or III.

The eradication of the carrier state itself may not be essential in the prevention of a subsequent attack of rheumatic fever. Thus in a preliminary study no instance of rheumatic fever was observed among eighty cases of streptococcal exudative tonsillitis or pharyngitis treated with aureomycin,<sup>10</sup> and treatment with this drug did not result in the eradication of the organism from the throat.\* Furthermore, as shown in the data on the control groups the incidence of positive cultures for group A streptococci taken approximately four weeks after the observed initiating infection is about 50 to 60 per cent in both those who develop rheumatic fever and those who do not develop this sequela. This evidence suggests but does not establish that eradication of the organism itself is not necessarily related to the prevention of rheumatic fever.

It is now well established that the antistreptolysin titers of sera from patients with acute rheumatic fever are elevated.<sup>17,18</sup> Furthermore, the antibody titer of sera collected during the convalescent period following a streptococcal infection is higher in those patients who develop rheumatic fever than in those who do not develop this complication.<sup>12,19</sup> Since the attack rate of

rheumatic fever in any population with acute streptococcal infections may be correlated with the magnitude of the antibody response,<sup>20</sup> it would appear that the ideal form of preventive therapy would be that which inhibited antibody production to the maximum degree.

The various drugs which have been used for therapy of streptococcal infections vary in their ability to suppress antibody production. Presumably the inhibition of antibody formation is related in some degree to inhibition of the streptococcus (antigen). The exhibition of the sulfonamide drugs to patients with streptococcal tonsillitis results in decreased numbers of streptococci and only a very slight suppression of antibody.<sup>13</sup> Treatment with these drugs does not prevent rheumatic fever.<sup>13</sup> Aureomycin therapy results in a marked decrease in the number of organisms that can be isolated on culture.<sup>21</sup> The degree of antibody inhibition is rather marked and preliminary studies indicate aureomycin therapy may result in a decreased incidence of rheumatic fever.<sup>10</sup> Penicillin administration, as has been recorded by a number of observers,<sup>2,19,23</sup> results in the eradication of the streptococcus, a reduction in antibody production and a decrease in the incidence of rheumatic fever.

There is a relationship between the dosage of penicillin and the degree of inhibition of antistreptolysin formation. A single injection of 600,000 units was less effective in this regard than two injections of 300,000 units seventy-two hours apart. Most effective was treatment schedule I in which therapy was continued for ninety-six hours. Kilbourne and Loge<sup>23</sup> observed significant increases in the antistreptolysin titer in the sera of 84 per cent of untreated patients, 64 per cent in patients treated with 300,000 units of aqueous penicillin once daily for six or seven days, and 14 per cent in patients treated with 20,000 to 50,000 units every three hours for four to seven days. The later dosage plan assured continuous levels of penicillin throughout the treatment period.

The time of institution of penicillin therapy would appear to be important in relation to inhibition of antibody. The data obtained, however, do not show that delay in therapy up to seventy-two hours after the onset of the illness results in a marked decrease in the degree of antibody inhibition. Further study is required to determine the relationship of the time of institution of therapy and the dose and duration

\* Subsequent studies have shown that aureomycin therapy results in the eradication of streptococci in many instances.



of treatment to the inhibition of antibody and to the prevention of rheumatic fever.

The decreased incidence of acute rheumatic fever following penicillin treatment of acute streptococcal infections observed in this study confirms previous studies<sup>1,2,23</sup> and is in disagreement with others.<sup>24-26</sup> Kilbourne and Loge<sup>23</sup> observed no rheumatic fever among twenty-nine patients treated with 20,000 to 50,000 units of penicillin every three hours for four to seven days. There were three cases of rheumatic fever among forty-seven patients treated with injections of 300,000 units of aqueous penicillin once daily for seven days and two cases among fifty-one untreated control patients. Massell, Sturgis, Knobloch, Streeter, Hall and Norcross in a recent report<sup>27</sup> observed only two cases of acute rheumatic fever following penicillin therapy of thirty-four streptococcal infections in rheumatic subjects. This is a marked reduction in the incidence of recurrent rheumatic fever since approximately 40 to 50 per cent of rheumatic subjects develop a recurrence following an untreated group A streptococcal infection.<sup>27</sup>

In contrast to the aforementioned favorable reports are the preliminary studies of Spink, Rantz, Boisvert and Coggeshall.<sup>24</sup> A total of fifty-nine soldiers with streptococcal tonsillitis or scarlet fever received varying dosages of aqueous penicillin in combination, in some patients, with sulfadiazine therapy. In this group six patients developed acute rheumatic fever. Analysis of the data on these six patients shows that the dose of penicillin was small, therapy was administered less than thirty-two hours in four of the patients and bacteriologic relapse or reinfection was observed in four patients.

Weinstein, Backrach and Boyer<sup>26</sup> treated 167 patients with scarlet fever with either intramuscular or oral penicillin for a period of ten days. In this group acute rheumatic fever was diagnosed in twelve instances, an incidence of 7.17 per cent. The authors conclude that treatment of scarlet fever with penicillin does not prevent rheumatic fever.

The outstanding differences between the studies of Weinstein<sup>26</sup> and those from the Streptococcal Disease Laboratory<sup>2</sup> have been detailed elsewhere.<sup>27,28</sup> The striking differences include the time interval from the onset of the observed infection to the onset of rheumatic fever and the criteria used in diagnosis. In the present study the average interval from onset of the acute respiratory illness to the onset of

rheumatic fever for all patients was fifty-one days in those that received penicillin and thirty-six days in the control group. This is in contrast to an average interval of 9.2 days observed by Weinstein.<sup>26</sup> This difference in the time interval may be due to the criteria used for dating the onset of rheumatic fever. Thus in Weinstein's studies<sup>26</sup> the criteria for onset included electrocardiographic abnormalities; those in the Wyoming study included only historical evidence.

The criteria used at the Streptococcal Disease Laboratory for the diagnosis of rheumatic fever were essentially those of Jones.<sup>9</sup> Weinstein *et al.*,<sup>26</sup> with more frequent electrocardiograms available, secured evidence of early electrocardiographic changes in many of their patients who failed to exhibit other symptoms or signs commonly associated with acute rheumatic fever. From the available evidence it is now possible to state only that penicillin therapy of acute streptococcal infections prevents the manifestations of rheumatic fever as defined in this study. Whether such therapy prevents the development of permanent cardiac damage was not determined, but the assumption should be that it may until otherwise established. Whether penicillin therapy will prevent early electrocardiographic changes in patients with streptococcal and other bacteriologic infections will have to be determined by further studies.

The importance of recognizing streptococcal infections is apparent for many cases of rheumatic fever should be prevented if adequate treatment is instituted. Streptococcal respiratory infections may be readily recognized without the employment of complicated laboratory procedures. The illnesses are characterized by the sudden onset of sore throat (soreness on swallowing) which is usually associated with constitutional reactions. Streptococcal respiratory infections in contrast to many non-bacterial respiratory infections are attended by a marked rise in temperature. The development of symptoms and fever usually reach a maximum degree about twenty-four hours after the onset.

The physical sign especially helpful in diagnosis is the presence of enlarged and tender cervical lymph nodes. The pharynx is diffusely injected, the lymphoid tissues and soft palate appear edematous, and exudative lesions are common. In those cases in which the diagnosis is doubtful a total leukocyte count should be obtained. If the leukocytes are increased to 10,000 or above, it is advisable to consider the

infection streptococcal in origin until proven otherwise. Occasionally cultures of the throat are required in the diagnosis of streptococcal respiratory infections when the previously described criteria are followed.

At the present time depot penicillin in dosages employed in this study may be used as outlined in schedule 1, or perhaps two injections of 600,000 units of depot penicillin administered seventy-two hours apart. The use of the sodium salt in doses of 15,000 to 25,000 units every three hours for eight to ten days might be employed for individuals who give a past history of rheumatic fever, because the incidence of recurrent rheumatic fever in such groups is high and such a schedule of treatment appears to be most effective in inhibiting antibody formation.<sup>23</sup>

#### SUMMARY

The prevention of acute rheumatic fever by penicillin therapy of acute streptococcal respiratory infections was attempted in this study. Procaine penicillin G in oil containing 2 per cent aluminum monostearate was injected intramuscularly according to one of three dosage schedules in 1,178 patients with exudative tonsillitis or pharyngitis while 1,162 patients remained untreated and served as controls.

There was a total of ten patients who had received penicillin and forty-two patients who received no treatment in whom an illness classified as definite or possible rheumatic fever subsequently developed.

Data collected on rheumatic subjects showed that reinfection with a new type of streptococcus frequently occurred when the interval between the onset of the observed attack of exudative tonsillitis or pharyngitis and the onset of rheumatic fever was prolonged. Excluding those cases of rheumatic fever developing after a forty-five-day interval between the two diseases results in two cases of rheumatic fever in the treated group and twenty-eight in the control patients. These data indicate that penicillin therapy of acute streptococcal infections almost completely prevents the subsequent occurrence of acute rheumatic fever.

Penicillin therapy was also found to eradicate the streptococcus from the oropharynx of the majority of individuals and to inhibit the formation of antistreptolysin. The most marked inhibition of antibody was that obtained by three injections of penicillin over a ninety-six-hour period totaling 1,200,000 units in comparison

to the suppression of antistreptolysin by either a single injection of 600,000 units or two injections of 300,000 units each given seventy-two hours apart.

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# Chloramphenicol in the Treatment of Meningococcal Meningitis\*

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CHLORAMPHENICOL possesses remarkable effectiveness as an antimicrobial drug particularly in the field of gram-negative infections. Its striking benefit in influenzal meningitis has been demonstrated by various investigators<sup>1,2</sup> who have shown that this antibiotic may be employed solely as the curative agent. We have endeavored to use a single antibiotic in the treatment of acute infections in spite of the rapidly growing tendency for dual and even triple therapy. Indeed, there is no clearcut clinical evidence except perhaps in tuberculous infections<sup>3</sup> and the enterococcal type of endocarditis<sup>19</sup> that supplemental therapy with an additional antibiotic is additive. Conversely, it appears that the use of two or more antibiotics may be harmful.<sup>4,5</sup> Until there is unmistakable evidence that the modes of action of various antibiotics are mediated through different mechanisms, it seems prudent to collect statistical data on the basis of one antibiotic alone, particularly when this course of therapy does not appear to jeopardize the condition of the patient.

With the knowledge that chloramphenicol was effective in a number of diseases caused by a gram-negative organism and that it possessed *in vitro* activity against *Neisseria intracellularis*<sup>6</sup> we performed additional *in vivo* and *in vitro* studies. Also, we administered chloramphenicol to fifteen patients with meningococcal meningitis. This report will present the results of these laboratory and clinical studies.

## EXPERIMENTAL STUDIES

**Methods.** Six strains of *Neisseria intracellularis* isolated from patients were utilized in these

studies. Three of these strains were type I, two were type II alpha and one was type II. These strains were identified by the usual gross and microscopic characteristics, biochemical and specific serologic reactions. Each strain was maintained in the laboratory by routine transfers on blood agar and by storage at  $-70^{\circ}\text{C}$ .

1. *Tests for in vitro sensitivity:* A serial dilution method using Fildes' broth was employed. The *in vitro* sensitivity of the organisms to aureomycin, chloramphenicol, penicillin and sulfadiazine was determined by the 100 per cent end point technic which has been previously described.<sup>2</sup>

2. *Animal studies:* Albino Swiss female mice ranging in weight from 15 to 20 gm. were employed for the chemotherapeutic tests. The infectious inoculum which was standardized by adjusting the optical density was prepared from eight-hour blood agar cultures. Serial tenfold dilutions of this suspension were then prepared and colony counts were performed on dilutions No. 7, 8 and 9. By this method rather consistent results were obtained (ten to the  $-7$ , 208 colonies, ten to the  $-8$ , 17 colonies and ten to the  $-9$ , 1 colony). A lethal inoculum of .2 ml. contained from 34 to 520 organisms. The inoculum was then suspended in 5 per cent mucin and injected intraperitoneally into mice. The animals were examined frequently and *N. intracellularis* was demonstrated routinely in the heart's blood of dying animals.

The various antibiotics† were given sub-

† The aureomycin, neomycin and terramycin used in this study were supplied by Lederle Laboratories Division, American Cyanamid Company, Merck and Company and Charles Pfizer and Company, respectively.

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cutaneously every four hours in the following doses: aureomycin 0.25 mg.; chloramphenicol 0.50 mg.; penicillin 0.20 mg.; sulfadiazine 3.0 mg.; neomycin 0.285 mg. and terramycin 0.50 mg. Therapy was initiated within three to four hours after inoculation and was continued for thirty-six hours. By this time the majority of the control animals had succumbed and the treated animals were markedly improved.

## RESULTS OF EXPERIMENTAL STUDIES

*In Vitro Studies.* In Table I are given the results of the *in vitro* sensitivity tests of the various antibiotics. It will be noted that with chloramphenicol the range of activity was from 0.62 to 2.5 gamma per cc. with the average sensitivity in the neighborhood of 1.5 gamma. The range of sensitivity to aureomycin was variable ranging from 0.40 to 7.5 gamma per cc. The average sensitivity with this antibiotic was higher than with chloramphenicol, averaging 3.7 gamma per cc. Four strains showed remarkable sensitivity

consistent. The range of activity of the five organisms tested was from 0.1 to 0.4 mg. per cc., average 0.2 mg. per cc. It is of interest that one strain, isolated from a patient who had not responded clinically to penicillin was penicillin sensitive when tested in the laboratory.

TABLE I  
IN VITRO SENSITIVITY OF *N. INTRACELLULARIS* TO VARIOUS ANTIBIOTICS

Strain No.	M.E.C.* Chloramphenicol (micrograms)	M.E.C. Aureomycin (micrograms)	M.E.C. Penicillin (units)	M.E.C. Sulfadiazine (mg.)
1	1.6	0.40	0.20	0.2
2	1.6	0.40	1.6	0.2
3	2.5	7.5	0.15	0.10
4	1.25	3.75	0.15	0.2
5	0.62	7.5	0.15	0.1
6	1.25	2.5	0.75	0.40

\*M.E.C. - Minimum effective concentration of antibiotic per milliliter of medium.

*In Vivo Studies.* In Table II are given the results obtained with the protection studies performed on two strains of *Neisseria intra-*

TABLE II  
CHEMOTHERAPEUTIC EFFECT OBTAINED IN MICE INFECTED WITH *N. INTRACELLULARIS*

Drug	Dose*	Graded Dilutions of Infectious Inoculum										
		mg./mouse	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>	10 <sup>-9</sup>	10 <sup>-10</sup>
<u>Experiment No.1</u>			<u>(Strain 2)</u>									
Aureomycin	.25		4/4 <sup>†</sup>	3/3	4/4	4/4	4/4	4/4	4/4	4/4		
Chloramphenicol	.50		1/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4		
Penicillin	.20		3/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4		
Sulfadiazine	3.0		2/4	1/4	3/4	4/4	4/4	4/4	4/4	4/4		
Neomycin	0.285 (50U)		2/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4		
Controls	...		...	0/4	0/4	0/4	0/4	2/4	2/4	4/4		
<u>Experiment No.2</u>			<u>(Strain 4)</u>									
Aureomycin	.25		0/4	0/4	2/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
Chloramphenicol	.50		0/4	0/4	2/4	2/4	4/4	4/4	4/4	4/4	4/4	4/4
Penicillin	.20		0/4	4/4	3/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
Sulfadiazine	3.0		0/4	0/4	2/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
Terramycin	.50		1/4	0/4	0/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4
Controls	...		0/4	0/4	0/4	0/4	0/4	0/4	0/4	1/4	2/4	4/4

\*Each animal was treated at six-hour intervals for thirty-six hours with the above dose.

†Numerator represents number of animals surviving; denominator, number of animals used in experiment.

{10<sup>-7</sup> 208/0.1 ml.  
 {10<sup>-8</sup> 17/0.1 ml.  
 {10<sup>-9</sup> 1/0.1 ml. } colony counts (Strain 2)

to penicillin whereas two of the six were moderately resistant, the range with this antibiotic being 0.15 to 1.6, average 0.5 units per cc. Results with sulfadiazine were slightly more

cellularis with various antibiotics tabulated. It will be noted that each agent employed was remarkably effective in controlling the experimental infection in mice. The degree of protec-

tion afforded by chloramphenicol ranged from  $10^{5.2}$  to  $10^{5.8}$  expressed as the protective index.\* The degree of protection afforded by aureomycin, penicillin, sulfadiazine, neomycin and terramycin was roughly comparable.

A brief summary of these findings demonstrated that the newer broad spectrum antibiotics, chloramphenicol, terramycin and aureomycin, appeared to be as effective as sulfadiazine and penicillin in the control of experimental mouse infection with *Neisseria intracellularis*.

#### CLINICAL APPRAISALS

*Method of Study. Selection of cases:* The patients presented in this study represent the cases diagnosed as meningococcal meningitis admitted to the medical and pediatric wards of the University Hospital between January, 1950, and February, 1951. Signs and symptoms typical of meningitis were present in each of these cases and in most instances the illness was of short duration. The age incidence in this group of fifteen cases ranged from ten months to forty-five years, average 9.3 years. A complicating disease unrelated to the primary illness was not present in any of these patients except Case 14 who had a sickle cell anemia crisis during his convalescence. Seven patients in this group were classified as severely ill and one showed signs of overwhelming meningococcemia. Two patients were presented to the ward showing paralysis of ocular muscles. Of this group eight had received treatment, without benefit, prior to admission. One patient had received approximately one million units of penicillin. The disease in this patient had progressed clinically and chemotherapy had not altered the bacteriologic picture in any of these patients.

*Diagnostic Criteria.* In addition to the clinical evidence of meningitis spinal fluid was examined immediately on admission. Total white blood cell counts were performed on the spinal fluid and after centrifugation the sediment was cultured and immediately examined with both Wright and Gram stains. The spinal fluid concentrations of glucose and protein were also determined. A tentative diagnosis of meningococcal meningitis was made in eleven of the fifteen cases after examination of the stained smear. Gram-negative organisms identified as *Neisseria intracellularis* were isolated in pure culture from each case reported. Specific typing technics revealed that four strains were type 1,

\* LD<sub>50</sub> control/LD<sub>50</sub> treated.

four were type II alpha and one was type II. Six strains were not typed. Blood and pharyngeal cultures were performed routinely and peripheral blood hemoglobin concentration and white blood cell counts were done. Urinalyses were performed in the usual manner.

*Method of Administration of Chloramphenicol.* Chloramphenicol was administered orally to children of all ages in doses of approximately 0.25 gm. at four-hour intervals (1.5 gm. daily); in adults the dose was 3.0 gm. daily (1 gm. every eight hours) after a large initial dose based on 50 mg. per kg. body weight. In five instances intravenous chloramphenicol\* was given in the early stages of treatment in an effort to achieve a high concentration of antibiotic in the blood and cerebrospinal fluid. The total amount of chloramphenicol administered to these fifteen patients varied from 5.5 to 30 gm. This dosage averaged 12.0 gm. given over a mean period of 5.6 days. In no instance was treatment continued longer than nine and a half days. (Table III.)

Frequently, simultaneous chloramphenicol concentrations of blood serum and spinal fluid were performed by methods previously described.<sup>7</sup> In all instances adequate concentrations were found in the blood and spinal fluids in patients receiving either the intravenous or the oral forms. The levels of antibiotic in the spinal fluid were roughly one-third to one-half that of the blood. Details of these findings are presented with the case records below.

#### CLINICAL RESULTS

*Results of Treatment.* Meningococcemia was demonstrated in three cases. Specimens of spinal fluid initially positive for meningococci in fifteen patients became sterile within thirty-six hours after the institution of specific therapy. Base line levels of glucose in the spinal fluid ranged from 0 to 60 mg. per 100 cc.; eight were 10 mg. or less. In practically all instances these concentrations had approached normal after twenty-four hours of specific therapy which, however, included the supplemental administration of intravenous glucose solutions. During the first forty-eight hours of therapy an elevation rather than a depression of the spinal fluid white cell count occurred in the majority of the cases. This increase in pleocytosis was not unduly alarming since meningococci were usually

\* Manufactured by Parke, Davis Company.



absent as determined by culture. Clearing of the spinal fluid occurred with surprising rapidity.

*Effects on the Clinical Course.* In all fifteen cases reported chloramphenicol produced a rapid return of the temperature to normal levels regardless of the severity of the disease or age

cranial nerves. This patient rapidly improved on chloramphenicol therapy. A third patient, not included in this series, also demonstrated a severe meningococcal septicemia. On admission the patient showed large petechial lesions over the body and was in a state of vascular collapse.

TABLE III

CHLORAMPHENICOL IN MENINGOCOCCIC MENINGITIS (TABULATION OF CASES)

Case	Sex	Age	Wgt. (kg.)	Chloramphenicol			Clinical Results		N. Intracellularis				Spinal Fluid	
				Duration of Treatment (days)	Total (gm.)	Day of Dis- ease Started	Duration Fever after Treat- ment (days)	Resi- duals	Pretreatment Blood	Sp. Pl.	Hour 1st Reg. Blood	Sp. Pl.	W.B.C.* (ag. S)	Sugar (ag. S)
1	M	1	10.7	5.5	8.75	3	3	None	0	Pos.	0	36	27.5	10
2	M	2.5	18.0	4.0	6.75	3	1.5	None	0	Pos.	0	16	17.5	2
3	M	45	66	4.0	18.0	4	3.0	None	0	Pos.	0	36	12.9	4
4	F	4	....	4.5	5.5	3	3.0	None	0	Pos.	0	24	13.9	29
5	M	6	....	6.0	11.0	3	2.0	None	0	Pos.	0	24	9.5	47
6	M	8	24	5.5	12.0	2	1.0	None	0	Pos.	0	18	5.0	57
7	M	36	60	2.5	5.5	1	2.0	None	0	Pos.	0	12	13.2	59
8	F	1.5	12.5	6.0	9.75	3	4.0	None	0	Pos.	0	16	8.3	0
9	M	19	....	5.5	30.0	3	2.0	None	Pos.	Pos.	24	24	5.9	8
10	M	7	20	9.0	16.0	1	2.5	None	Pos.	Pos.	24	24	6.6	31
11	M	2	14	9.0	14.5	5	4.0	Yes	Pos.	Pos.	24	24	11.2	0
12	M	1	10.0	7.0	22.0	4	1.5	None	0	Pos.	0	10	16.9	13
13	M	10 mo.	11.0	5.5	8.75	3	2.75	None	0	Pos.	0	28	11.1	10.0
14	M	2.5	14.0	8.5	15.0	1	4.5	None	0	Pos.	0	16	9.8	60.0
15	M	3.0	14.0	9.5	12.5	4	4.5	Yes	0	Pos.	0	20	11.3	0

\*Expressed as thousands per cu. mm.

of the patient. The temperatures reached normal on the average of three and a half days, range one to four and a half days. (Table III.) In six instances during the convalescent period, sporadic elevations of temperature were noted but were not indicative of a relapse.

There was remarkable improvement of the bedside appearance of these patients within the first twenty-four hours of treatment. The headache had largely abated and after the third day convalescence proceeded uneventfully.

One patient (Case 10) was severely ill with meningitis and presented the clinical picture of the Waterhouse-Friderichsen's syndrome. In addition to antibiotic therapy which was administered intravenously, the patient received generous quantities of intravenous saline solution as well as adrenal cortical extract. Improvement was striking and within a period of thirty-six hours he was sitting up in bed and eating voluntarily. The second patient (Case 11) demonstrated clinical signs of meningococcemia and on admission also presented signs indicative of paralysis of the right and left third and sixth

Although penicillin had been administered prior to hospitalization, the clinical condition was critical. Treatment consisted of intravenous chloramphenicol, intravenous salt solution and adrenal cortical extract. Improvement in this patient was likewise striking.

#### ILLUSTRATIVE CASE REPORTS

**CASE 13.** This patient, a ten month old white male infant, was admitted with marked irritability, fever and vomiting. He had received 300,000 units of penicillin ten days prior to admission because of fever and sore throat. Three days prior to admission the fever had returned and the patient became progressively more irritable and lethargic.

On first examination in the hospital he was lethargic and quite irritable. Temperature was 101.6°F., pulse 180 per minute. The skin was hot and dry but no petechiae were noted. There was marked injection of both tonsils and pharynx. Nuchal rigidity was marked and Brudzinski's and Kernig's signs were positive. The pupils were equal and reactive and on funduscopy

examination both optic nerves were normal. The deep reflexes were hyperactive.

Spinal fluid was grossly cloudy and contained 11,100 white blood cells per cu. mm. A few gram-negative diplococci were seen on a direct smear. The initial glucose determination was

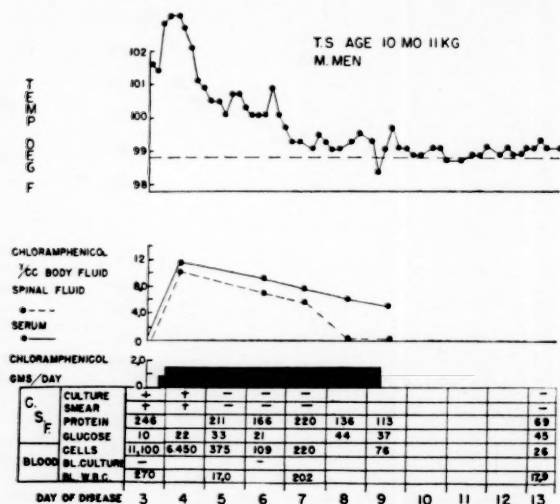


FIG. 1. Case 13. Chart of results in ten month old patient with meningococcal meningitis treated with chloramphenicol.

10 mg. per 100 cc. Chloramphenicol was administered orally with an initial dose of 750 mg. followed by 250 mg. at four-hour intervals. Treatment was continued for five days with a total dose of 8.75 gm. There was marked improvement within twenty-four hours and by the fourth day the patient was relatively asymptomatic. He was discharged from the hospital without evidence of residuals. Pertinent clinical and laboratory findings are presented in Figure 1.

**CASE 3.** This patient, a forty-five year old white male, was hospitalized because of severe headache, chills, fever and drowsiness. Four days prior to admission he noted a dull headache and moderate fever which was accompanied by a chill. There was progressive increase in the headache, anorexia, slurring of speech and blurring of vision.

Physical examination revealed an acutely ill, lethargic male with marked nuchal rigidity. Skin was dry but without petechiae. Kernig's and Brudzinski's signs were positive. There were no pathologic reflexes.

Lumbar puncture revealed grossly cloudy fluid which contained several gram-negative diplococci. A tentative diagnosis of meningococcal meningitis was made and the patient

received 3.0 gm. of chloramphenicol followed by 3.0 gm. daily for a total dosage of 18.0 gm.

Spinal fluid cultures produced *N. intracellularis* type I and *D. pneumoniae*, type XIX. Cerebrospinal fluid obtained the following day (eighteen hours after admission) revealed a few

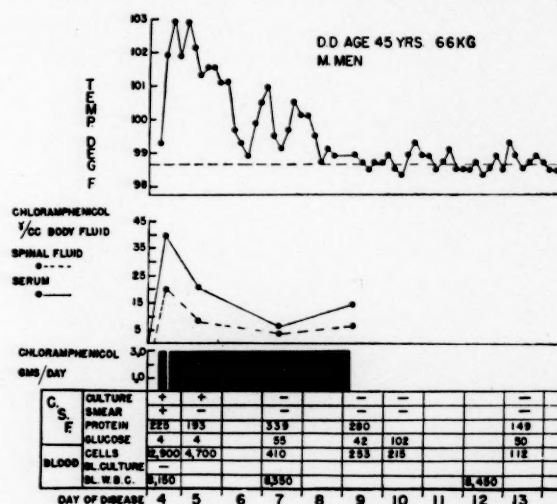


FIG. 2. Case 3. Chart of course in an adult treated with chloramphenicol for meningococcal meningitis.

meningococci. Cultures were sterile after forty-eight hours. Leukocyte counts ranged from 4,700 to 12,900 during the acute phase of the disease. The initial glucose concentration was 4 mg. per cent which subsequently returned to normal in forty-eight hours. Blood cultures were sterile and meningococci were not isolated from the pharynx.

The clinical course was satisfactory and although slurred speech and nuchal rigidity persisted for several days, the patient became free of symptoms after three days of specific therapy. Roentgen examination of his sinus revealed right antritis. There was progressive improvement until discharge on the twentieth hospital day. (Fig. 2.)

**CASE 8.** The patient, a nineteen month old female child, became ill with high fever, stiffness of the neck and stupor two days prior to admission. Three days prior to admission the patient had been seen by a private physician who made a tentative diagnosis of pneumonia and administered 300,000 units of penicillin intramuscularly and 450,000 units orally. The irritability, stupor and fever progressed. Six hours prior to admission 300,000 units of penicillin were given intramuscularly.



On admission the child was acutely ill, very lethargic and responded only to painful stimuli. There were obvious signs of meningeal irritation and a few petechiae were noted on the buccal mucosa. The initial lumbar puncture produced densely cloudy cerebrospinal fluid containing 8,300 white blood cells and 0 mg. of glucose per 100 cc. Cultures of this fluid ultimately produced a pure growth of *Neisseria intracellularis*, type II alpha. The patient received an initial dose of 0.5 gm. of chloramphenicol intravenously followed by doses of 250 mg. orally every four hours for a total period of six days. There was rapid improvement in this patient manifested by lessening of the irritability and improvement of the general strength and vigor. By the fifth hospital day all signs of meningeal irritation had cleared and the neck was flexible. Spinal fluid obtained after sixteen hours of chloramphenicol therapy was sterile. Furthermore, it is of interest that on admission to the hospital *Neisseria intracellularis* were isolated from the nasopharynx. A culture taken after chloramphenicol therapy was completed was negative for this organism. The patient was discharged free of symptoms on her fifteenth hospital day.

**CASE 10.** This patient, a seven year old white male, first became ill fifteen hours prior to admission when he complained of fever, headache and nuchal pain. Four hours later a diffuse purpuric cutaneous eruption appeared. He was admitted to the University Hospital eleven hours later in a state of profound circulatory collapse. The eruption had become quite diffuse and the patient was unconscious.

Physical examination on admission revealed a comatose male in marked circulatory distress. Pulse was not obtainable and blood pressure was recorded as 40/0. There were petechiae over the entire cutaneous surface, mucous membranes of the mouth and conjunctivae. The pharynx was slightly injected. The heart rate was rapid and the sounds distant. The lungs were clear. There was moderate nuchal rigidity and Kernig's sign was positive.

Lumbar puncture revealed cloudy spinal fluid which contained 6,675 leukocytes and 31 mg. of glucose. Numerous gram-negative diplococci were seen on examination of the direct spinal fluid smear.

The patient received supportive intravenous therapy including blood, saline solution and adrenal cortical extract in the dosage of 5 cc. every six hours for the first twenty-four hours.

Chloramphenicol was given via the intravenous route during the first hospital day. The clinical response was dramatic and by the second hospital day the patient was markedly improved. (Blood pressure was normal after several hours of therapy.) A total of 16 gm. of chloramphenicol was given.

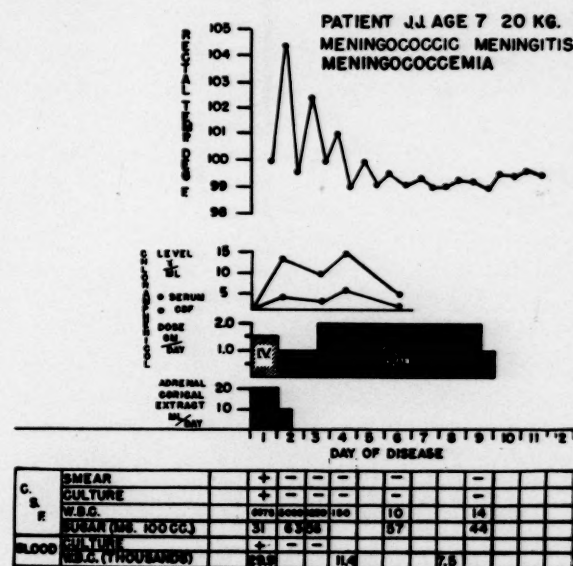


FIG. 3. Case 10. Graphic record of a case of meningococcemia and meningitis in a seven year old boy treated with chloramphenicol.

*Neisseria intracellularis*, type I, was isolated from the blood, spinal fluid and nasopharynx on admission. Blood and spinal fluid were sterile twenty-four hours after the institution of specific antibiotic therapy. Cytologic response of the spinal fluid was excellent. The details of the clinical course can be seen in Figure 3.

#### COMMENTS AND SUMMARY

The investigations of McLean and associates<sup>6</sup> revealed that chloramphenicol exerts significant activity against *N. intracellularis* when tested *in vitro*. Our studies confirm these findings and show that in the experimentally infected mouse a high level of protection is afforded by chloramphenicol. Indeed, under these *in vivo* conditions it appears that the newer broad spectrum antibiotics (terramycin, aureomycin, chloramphenicol as well as neomycin) equal the striking effects of penicillin and sulfadiazine.<sup>8,9</sup> Neomycin is probably the least interesting in this respect because of the relative toxic sequelae which follow administration of this drug.<sup>10</sup>

There is an increasing tendency to adminis-



ter two or more antibiotics simultaneously in severe clinical infections on the assumption that if one antibiotic is effective perhaps another antibiotic may be doubly effective. This reasoning does not appear to be based upon adequate clinical evidence and until additional information is gained pertaining particularly to the modes of action of antibiotics there appears to be little rationale in complicating therapy in most clinical infections. Moreover, the work of Jawetz<sup>4,5</sup> has shown an antagonistic action when penicillin and chloramphenicol are combined.

It has been demonstrated<sup>1,2</sup> that chloramphenicol possesses remarkable effectiveness when used in the influenzal meningitis of infants. This simplified form of therapy appears to be as effective as the combined treatment with streptomycin, sulfadiazine and hyperimmune rabbit serum.<sup>11</sup>

We consider it important to determine the true range of the newer antibiotics because of the of the resultant simplification of therapeutic regimens. Moreover, the rapidity with which the newer antibiotics alter the bacteriologic picture through their suppressive effects have made it unnecessary to combine several antibiotics in diseases such as typhoid fever,<sup>12</sup> tularemia,<sup>13</sup> the acute manifestations of brucellosis,<sup>14,15</sup> pneumonia<sup>16</sup> and in the rickettsioses.<sup>17,18</sup> It is realized that such generalizations do not hold for various disease entities. Each pathogen and the underlying pathologic process must be considered in its own light.

Penicillin and sulfadiazine have strikingly lowered the fatality rates of meningococcal meningitis from a formerly highly fatal disease to one with a fatality of less than 10 per cent. Furthermore, it is unlikely that additional antibiotic agents will significantly reduce this mortality rate since diagnoses are often made late in the course of disease after irreparable damage exists. On the other hand, the practical significance of the effectiveness of chloramphenicol in meningococcal infections is apparent. Given an infant with purulent meningitis in whom a bacteriologic diagnosis is not yet obtained the administration of penicillin could be hazardous in some instances since infant meningitis frequently is caused by *H. influenza* or *N. intracellularis*. The blind administration of sulfadiazine and/or penicillin under these conditions would be adequate for meningitis caused by meningococci but totally inadequate for meningitis caused by *H. influenzae*. The delay in

institution of proper therapy could result in the development of irreversible tissue changes. Thus chloramphenicol with its dual action in influenzal and meningococcal meningitis would suffice for these two types of infection. Pneumococcal meningitis will usually be apparent through the finding of gram-positive diplococci in the initial smear. Penicillin may be administered under these conditions. Efforts pertaining to the making of a specific etiologic diagnosis cannot be overemphasized.

Our findings in fifteen patients with meningococcal meningitis indicates that chloramphenicol is an effective weapon. A suitable control series with penicillin was not included because of the small number of available cases. A survey of the patients with this disease who entered the University Hospital during the years from 1944 to 1948 revealed that in thirty-one cases the duration of fever was 4.8 days after institution of penicillin therapy. These patients are not bona fide controls but nevertheless 4.8 days of fever in the penicillin group is closely comparable to 3.5 days of fever in the chloramphenicol-treated series. In thirty-five patients treated with penicillin and sulfadiazine there were three fatalities. There were no fatalities in the fifteen patients receiving chloramphenicol nor were there residual signs of meningitis except in one patient (Case 11) who showed ophthalmoplegia before antibiotic treatment was instituted. This eventually cleared.

An optimal therapeutic regimen cannot be determined from the results obtained in so few cases and additional studies on the subject are necessary. Nevertheless, it appears that when chloramphenicol is tolerated orally an initial dose based on approximately 100 mg. per kg. body of weight and subsequent doses of approximately 75 to 100 mg. per kg. body weight per day is sufficient. In practice an initial adult dose of 3 gm. followed by doses of 1 gm. every eight hours is usually adequate. Children require approximately one-half to two-thirds the adult dose. We have found intravenous chloramphenicol helpful in providing a prompt high therapeutic level when administered in doses based on approximately 50 mg. per g. of body weight per day. There is no difficulty in administration and intravenous therapy may be continued until oral medication is practical. For adults we have employed a dose of approximately 0.5 gm. every six hours; children have received approximately one-half the adult dose.

## CONCLUSIONS

Fifteen infant and adult patients with meningococcal meningitis made rapid recoveries after chloramphenicol treatment. The clinical and bacteriologic response to therapy was striking. One patient showing fulminant meningococcemia and meningitis responded very favorably to chloramphenicol. The need for adequate data on therapy with individual antibiotics has been emphasized.

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# An Evaluation of the Hemagglutination Test for Tuberculosis\*

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WIDESPREAD interest in the Middlebrook-Dubos hemagglutination test for antibodies to certain polysaccharide fractions of tubercle bacilli is testimony to the great need of such a test. The authors<sup>1</sup> found a high degree of specificity for it. Dubos<sup>2</sup> and Middlebrook<sup>3</sup> on the basis of theoretic considerations and the reports of early trials suggest that a positive reaction at 1:8 dilution may be presumptive evidence of disease. Gernez-Rieux and Tacquet<sup>4</sup> obtained encouraging results with an antigen extracted from tubercle bacilli. Rothbard<sup>5</sup> using an old tuberculin antigen finds that the presence of agglutinins is evidently related to the activity of the disease and on this basis there might be hope of the test being of prognostic value. Smith and Scott,<sup>6</sup> on the other hand, using a somewhat simplified method do not find the test useful for determining clinical activity and report that the sera of normal adults as well as of patients ill with non-tuberculous disease may have hemagglutination titers. For the most part these titers were correlated with positive tuberculin reactions or with stimulation thought to result from tuberculin testing. Sohier<sup>7</sup> used a tuberculin antigen and found nineteen of 140 normal young adults to give a positive hemagglutination reaction and nine of seventeen cases of active tuberculosis to be negative but concluded that his results on the whole were satisfactory.

The hemagglutination test is the latest of a series of agglutination tests that have been proposed for use in the laboratory

study of tuberculosis. In 1898 Arloing and Courmont<sup>8</sup> recommended the use of a glycerol suspension of a special strain of tubercle bacilli. Sohier<sup>9</sup> has recently reviewed this test and some modifications of it and concludes that it may be of limited value. Cannon and Marshall in 1940<sup>10</sup> suggested the use of collodion particles coated with an antigen derived from the tubercle bacillus. Weir<sup>11</sup> applied this test to rabbit and human sera and reported encouraging results. Later, bacteria were substituted for collodion particles as adsorbents of tuberculin antigen (Reuther and MacDonald<sup>12</sup>). None of these tests has as yet found general acceptance.

Cummings, Fleming and Runyon<sup>18</sup> made a preliminary investigation of the Middlebrook-Dubos hemagglutination reaction with sera from rabbits before and after injection of tubercle bacilli, heat-killed tubercle bacilli and BCG. The results were encouraging enough to warrant extensive evaluation employing human sera from normal tuberculin-negative individuals, normal tuberculin-positive reactors, cases of active tuberculosis, BCG-vaccinated individuals and from patients with related diseases such as sarcoidosis and pulmonary mycoses. A group of patients with other diseases which are known at times to give false-positive serologic reactions was also studied.

## METHODS

Sera were obtained from patients associated with Lawson V. A. Hospital, Veterans Administration Hospital 48, Georgia State Depart-

\* From the Lawson V. A. Hospital, Chamblee, Ga. and Emory Univ. School of Medicine, Atlanta, Ga. Published with the permission of the Chief Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.



ment of Health, Grady Memorial Hospital, Emory University Hospital, private physicians, Atlanta, Georgia, and City-County Health Department of Columbus, Georgia.

The procedure adhered to for all of the tests reported herein was essentially that of Scott and Smith,<sup>13</sup> the antigen being the Lederle 4X tuberculin.\* Simple 0.85 per cent sodium chloride solution was used instead of the buffered saline employed by Smith and Scott. Preliminary tests with saline solutions at pH 6.2 and 7.8 gave identical titers with the same sera indicating that pH changes in this range would not affect the readings. All the tests were read macroscopically and by the same persons, without knowledge of the identity of the sera. Included with each series of tests were three types of controls: (1) sensitized red cells plus saline; no serum; (2) serum plus non-sensitized cells; (3) a serum of known titer (previously tested).

Since in the first tube of a test serum previously diluted 1:2 is further diluted with an equal volume of antigen suspension, the lowest dilution of serum tested is 1:4. This is evidently true, also, of the work of previous investigators who, however, have expressed their results in terms of the dilution of serum before addition of antigen. The titer designation used here represents the final dilution of serum in the test so that our 1:16, for example, is equivalent to the 1:8 of Dubos and other writers.

A simplification of the procedure for absorbing heterophile antibodies recommended by Middlebrook<sup>14</sup> was adopted during the course of the investigation.

#### RESULTS

Repeated tests on the same serum show that the method used gives consistent results. (Table I.) We have obtained no difference greater than corresponds to two tubes; 98 per cent of the tests gave identical titers or were only one tube apart. Titers on consecutive sera from the same person, too, have in general followed a consistent course.

A summary of the results of 423 tests is given in Table II. It is immediately apparent that there was no group without titer; the lowest mean titer was for normal tuberculin-negative children; the groups having

the highest average titers were those with far advanced tuberculosis; but most striking, individual titers in any group are scattered quite widely.

*Normal Adults.* The hemagglutination titers of fifty-three normal adults, mostly laboratory workers or medical students with

TABLE I  
RESULTS OF TWO TESTS ON EACH OF FORTY-SIX POSITIVE  
SERA USING DIFFERENT LOTS OF SENSITIZED CELLS

	Num- ber	Per- cent- age
Identical titer, 1st and 2nd test . . . . .	28	61
One-tube difference . . . . .	17	37
Two-tube difference . . . . .	1	2
More than two-tube difference . . . . .	0	0

possible exposure to tuberculosis, were determined. The mean titer of the seventeen tuberculin-positive healthy adults averaged 1:9. Most of the titers were low or negative but in each group there was an individual who had a titer of 1:64. Each of these subjects and five of the six individuals with titers of 1:32 were laboratory workers with possible exposure to tubercle bacilli.

*Children.* One hundred four normal children who had no known exposure to tuberculosis were tested. Eighty were tuberculin-negative and of these fifty-one had no demonstrable hemagglutination titer. One had a titer of 1:32. The average was 1:3. The twenty-four tuberculin-positive children were found to have an average titer of 1:2.

Seven children had a clinical diagnosis of pulmonary tuberculosis. All of these were tuberculin positive but in some cases the diagnosis was not substantiated by the demonstration of tubercle bacilli. Most of the titers were low or negative and the average titer was 1:7. Sera from those children with titers of 1:32 and 1:128, respectively, were obtained after these patients had had prolonged treatment and were considered to be arrested cases.

Although tuberculosis was not proven in all of the aforementioned children, in the

\* Obtained from Lederle Laboratories, Pearl River, N. Y.

following cases of pulmonary tuberculosis in adults all of those considered to be active had definitely demonstrable tubercle bacilli.

*Minimal Tuberculosis.* Fifteen persons with active minimal tuberculosis were tested. All sera of this group had hemagglutination

*Moderately Advanced Tuberculosis.* The titers of sera from fifty-four active cases averaged 1:17. Those having definite cavitation did not show a higher titer (average 1:14) than those without cavity (average 1:17). Six cases of inactive disease included only

TABLE II  
DISTRIBUTION OF HEMAGGLUTINATION TITERS

Condition	No. of Patients	Mean Titer	No. of Patients with Titers of:							Tuberculin Test		
			0	1:4	1:8	1:16	1:32	1:64	1:128	+	-	Not Done
Normal adults (tuberculin negative) . . . . .	35	1:5	15	5	8	4	2	1	0	0	35	0
Normal adults (tuberculin positive) . . . . .	18	1:9	6	0	4	2	5	1	0	18	0	0
Normal children (tuberculin negative) . . . . .	80	1:3	51	7	14	7	1	0	0	0	80	0
Normal children (tuberculin positive) . . . . .	24	1:2	16	5	2	1	0	0	0	24	0	0
Pulmonary tuberculosis, children . . . . .	7	1:7	3	2	0	0	1	0	1	7	0	0
Pulmonary tuberculosis, adults												
Minimal . . . . .	29	1:18	1	4	6	5	8	4	1	26	0	3
Active . . . . .	15	1:19	0	3	3	2	3	3	1	12	0	3
Inactive . . . . .	14	1:16	1	1	3	3	5	1	0	14	0	0
Moderately advanced tuberculosis . . . . .	60	1:16	4	12	12	6	5	6	5	46	0	14
Active . . . . .	54	1:17	3	10	11	6	13	6	5	42	0	12
Inactive . . . . .	6	1:13	1	2	1	0	2	0	0	4	0	2
Cavity definite . . . . .	27	1:14	3	7	3	3	6	3	2	19	0	8
No cavity . . . . .	33	1:17	1	5	9	3	9	3	3	27	0	6
Far advanced tuberculosis . . . . .	46	1:26	2	2	7	14	6	6	9	44	1	1
Active . . . . .	40	1:28	0	2	5	14	6	5	8	38	1	1
Inactive . . . . .	6	1:12	2	0	2	0	0	1	1	6	0	0
Cavity . . . . .	30	1:31	0	1	4	8	6	4	7	29	1	0
No cavity . . . . .	16	1:16	2	1	3	6	0	2	2	15	0	1
Extrapulmonary tuberculosis . . . . .	24	1:12	4	2	5	2	8	1	1	16	0	8
Pleural effusion . . . . .	4	1:16	0	1	0	1	2	0	0	4	0	0
Pericardial effusion . . . . .	6	1:16	0	0	1	1	3	1	0	2	0	4
Meningitis . . . . .	5	1:11	2	0	1	0	1	0	1	2	0	3
Miliary . . . . .	2	1:4	1	0	1	0	0	0	0	2	0	0
Bone, joint . . . . .	4	1:16	0	0	2	0	2	0	0	4	0	0
Sinus . . . . .	1	0	1	0	0	0	0	0	0	1	0	0
Genitourinary tract . . . . .	1	1:4	0	1	0	0	0	0	0	0	0	1
Lymph node . . . . .	1	0	1	0	0	0	0	0	0	1	0	0
Sarcoidosis . . . . .	22	1:7	7	3	3	7	1	1	0	2	19	1
Active . . . . .	17	1:6	6	3	2	5	0	1	0	2	14	1
Inactive . . . . .	5	1:11	1	0	1	2	1	0	0	0	5	0
Syphilis . . . . .	15	1:5	5	4	2	2	1	1	0	4	3	8
Miscellaneous pulmonary diseases . . . . .	23	1:6	6	4	7	5	1	0	0	14	1	8
Miscellaneous diseases . . . . .	40	1:5	16	11	8	2	3	0	0	..	..	..

titers, two of them high (1:128 and 1:64). The average titer in this group was 1:19, with an equal distribution of cases above and below the mean.

Fourteen persons with inactive disease were studied. Five had titers of 1:32. The average titer, 1:16, was only slightly less than the average titer for active disease.

two with titers of 1:32. The remaining titers were lower or negative.

Three patients with active cavitory disease and one with inactive non-cavitory disease had no demonstrable hemagglutination titer.

*Far Advanced Tuberculosis.* The average titer of sera from forty patients with active



far advanced tuberculosis was 1:28. Thirty of these patients had definite cavitation, seven had titers of 1:128, four had titers of 1:64 and six had titers of 1:32, the average being 1:31. In a group of sixteen cases in which cavitation was not determined or not present the average titer was 1:16; one patient had a titer of 1:128 and one had a titer of 1:64.

There was no active case with a negative hemagglutination titer. Titers of four of the six inactive cases were 1:128, 1:64, 1:8 and 1:8; the other two were negative. The patient with the titer of 1:128 had been asymptomatic for over two years following a thoracoplasty, and three gastric washings at the time of hemagglutination testing failed to produce tubercle bacilli by guinea pig inoculation or culture.

In a group of eight patients with cavitary silicotuberculosis (all active except one) one had a titer of 1:128 and one a titer of 1:64. The remaining titers were low but the average was 1:26.

*Extrapulmonary Tuberculosis.* In these cases although isolation of the tubercle bacillus was not accomplished in some instances, the clinical course of the patients strongly indicated a tuberculous etiology. Two of four patients with pleural effusion had titers of 1:32; the average titer was 1:16. Six patients with pericardial effusions had an average titer of 1:16; one had a titer of 1:64 and three others had titers of 1:32. In a group of five individuals with tuberculous meningitis there was one with a titer of 1:128, one with 1:32, one with 1:8 and two with no titer. The average titer was 1:11. One case of miliary tuberculosis in a child who responded well to streptomycin treatment had a titer of 1:8 after treatment. Unfortunately no test was performed prior to therapy. Four patients with Pott's disease had titers between 1:8 and 1:32. One patient with tuberculosis with a draining sinus had no titer. One patient with genitourinary tract infection had a titer of 1:4.

*Sarcoidosis.* Twenty-two cases of sarcoidosis proven by biopsy were studied. Titers ranged from zero to 1:64, the average being

1:8. Although it is difficult to assay clinical activity in these patients, seventeen cases were considered "active." The spectrum of titers was essentially the same in this group and the average titer was 1:7. Five "inactive" or "questionably active" cases had an average titer of 1:11; all five of these latter cases were tuberculin-negative. Only two patients with sarcoidosis had positive tuberculin tests; their hemagglutination titers were 1:16 and 1:64 in contrast to the 1:7 average for the nineteen tuberculin-negative patients.

*Syphilis.* Hemagglutination tests were performed in fifteen patients in whom the diagnosis of syphilis had been confirmed serologically. Four were undergoing penicillin therapy and three of these had reverted to a negative Kahn reaction. The titer spectrum was similar to that of "normal" adults, with one titer of 1:64, one with a titer of 1:32 and five with negative titers. The average titer was 1:5.

*Miscellaneous Pulmonary Diseases.* This group of twenty-three patients included cases of chronic bronchitis, bronchiectasis, emphysema, bronchogenic carcinoma, asthma, pulmonary infarction, nocardiosis, blastomycosis, coccidioidomycosis, silicosis, lung abscess, pneumococcal and atypical pneumonia. Only one patient had a titer as high as 1:32 (bronchiectasis) and six had no titer. The average titer was 1:6.

*Miscellaneous Diseases.* This group of forty patients included the usual array of infectious, degenerative, neoplastic and metabolic diseases seen in a general hospital. Only three had titers as high as 1:32 and sixteen were without titers. The average titer was 1:5.

*BCG-vaccinated Adults.* Eleven nurses, all of whom were tuberculin-negative, were vaccinated with BCG according to the multiple puncture method of Rosenthal. In all, the BCG vaccination successfully produced papules at the sites of inoculation within six weeks. (Table III.) At this time all of the patients had converted to tuberculin positivity and all had hemagglutination titers. A two-tube rise in titer occurred in



four of the ten tested at six weeks. Tests done six months after BCG inoculation showed no significant changes in titer in any of the subjects tested. Unfortunately five of the subjects were not available at this time and the series is too small to be conclusive. It

TABLE III  
RESPONSE TO BCG VACCINATION

Before Vaccination			After BCG Vaccination			
Case	Titer	Skin Test	3 Weeks	6 Weeks		6 Months
			Titer	Titer	Skin Test	Titer
1	1:16	—	1:4	1:64	+	1:32
2	Negative	—	Negative	1:8	+	N. D. *
3	1:8	—	1:8	1:32	+	1:32
4	1:8	—	1:4	1:32	+	N. D.
5	Negative	—	Negative	1:4	+	Negative
6	1:8	—	1:4	1:8	+	1:4
7	1:16	—	1:8	1:32	+	1:32
8	1:4	—	Negative	1:4	+	1:4
9	1:16	—	1:4	1:8	+	N. D.
10	1:8	—	1:8	N. D.	+	N. D.
11	1:8	—	Negative	1:4	+	N. D.
Average	1:7	—	1:4	1:13	+	1:10

\* N. D. = not done, patient not available for testing.

was of interest that the Negro nurses had more skin reaction to the vaccine and tuberculin test but no correlation was noted with the degree of hemagglutination response.

#### COMMENTS

Although there was a significant difference between the average titer of the normal group and that of the active cases of pulmonary tuberculosis, both groups had many low titers. Since a low titer does not rule out disease, the question arises: What is a significant titer above which tuberculous disease is suspected? Dubos<sup>2</sup> and Middlebrook<sup>3</sup> suggest that 1:8 (our 1:16) may be significant of active tuberculosis. In our series it is evident that a titer to be significant of tuberculosis must be definitely greater than 1:8, at least 1:32. It was inter-

esting to note that in the normal groups the two subjects with titers of 1:64 and five of the seven cases with titers of 1:32 were laboratory technicians intimately associated with tuberculosis work. Thus titers of over 1:32 may be only suggestive of tuberculous disease.

Titers of 1:32 and 1:64 found in normal individuals and patients with non-tuberculous disease (Table II) do not support Dubos' hypothesis<sup>2</sup> that hemagglutinins represent a response to actively growing tubercle bacilli. These findings do not, however, deny the hypothesis for they may represent reactions to non-specific components of the crude old tuberculin antigen. The same remarks apply to the positive hemagglutinations reported by Sohler for normal young adults.

Rich<sup>15</sup> has maintained that there is no established relation between tuberculin skin sensitivity and the presence of circulating antibodies to the tubercle bacillus. Dubos<sup>2</sup> points out that while tuberculin hypersensitivity is long-lasting, hemagglutinins may disappear as tubercle bacilli become quiescent in the body. Hemagglutination antigens as well as tuberculin antigens occur in old tuberculin but they may be different antigens and the tests would not be expected to run parallel. Our results indeed show no consistent relationship between the two tests although averaged titers of tuberculin-positive adult groups are greater than for tuberculin-negative groups. Sohler reports 73 per cent disagreements between tuberculin and hemagglutinin reactions.<sup>7</sup> Smith and Scott<sup>6</sup> have observed that hemagglutination titers are higher in individuals following tuberculin skin testing. We have seen evidence of this, also, but it was not found in two of our cases who were followed with serial hemagglutination tests after severe skin reactions.

With regard to diagnosis or determination of activity of tuberculosis it is apparent in our series that the test failed at times when it could be most useful, that is, in cases of extrapulmonary tuberculosis and in some cases of early pulmonary tuberculosis. Only two of twenty-four patients with extra-

pulmonary disease had titers above 1:32; eight had titers of 1:32.

In general patients with inactive pulmonary tuberculosis of all categories had lower average titers than did the active cases; however, one established inactive case (cited before) showed agglutinins in a serum diluted 1:128.

The test would seem to be of little value in differentiating degrees of severity of pulmonary tuberculosis since every titer is represented in each of the groups. It is true that in far advanced disease the highest average titer (1:28) of any group was found and those patients with cavities had a higher average titer (1:31) than those without cavities (1:19). However, the average titers for minimal (1:19) and for moderately advanced disease (1:15) are not significantly different. Most difficult to explain is the large number of negative or low titers in patients with active tuberculosis. Repeated tests in the same individuals may be of more significance than an average titer of several patients.

Fourteen patients with far advanced and moderately advanced tuberculosis were followed up over a period of eight months to determine the influence of the course of the disease, time and treatment upon the hemagglutination antibodies. In the sera of three patients who showed a downhill course over this period in spite of chemotherapy there was diminution of antibody titers after early rises; after eight months there had been a two-tube fall in titer in each case. The other patients showed gradual improvement; five of them had titers remaining essentially the same during the eight months, three had minimal rises after eight months and three had minimal falls during that time. In this larger group which showed satisfactory improvement all received chemotherapy except four. In these four cases titers went down in two, up in one and remained essentially the same in the other. Thus there was no obvious response of the hemagglutination antibodies to progression or regression of disease or to chemotherapy in this small group.

Other tests<sup>16</sup> have shown that patients with sarcoidosis have a serologic pattern quite different from that of tuberculosis and that their titer distribution is more like that of normal individuals. The average titer (1:8) of our patients with sarcoidosis agrees with this observation. "Activity" of the disease in our patients was not associated with a higher average titer than "inactivity." It was of interest to note that in the sera of three sarcoid patients who were treated with cortisone there was a two-tube fall in titer after a month of treatment in each case.

Following BCG vaccination there were rather inconsistent responses of the hemagglutination titer. The titers in most of the cases remained essentially the same while about a third of the cases had two-tube rises. All patients converted to tuberculin positivity after vaccination. The determinations were done three weeks, six weeks and six months following BCG vaccinations. This failure of correlation of antibody titer and appearance of skin sensitivity fits in with our preliminary evaluation<sup>17</sup> of the test applied to over 200 school children participating in the Columbus, Georgia, BCG trial.\* However, in studies with rabbits<sup>18</sup> there was a definite rise in hemagglutination titer concomitant with development of tuberculin positivity three weeks after BCG vaccination and the elevation was persistent for several months.

#### SUMMARY

1. A clinical evaluation was made of the Scott and Smith modification of the hemagglutination test for tuberculosis in normal individuals and in subjects with tuberculosis, sarcoidosis, following BCG vaccination and with miscellaneous diseases. Tests were performed on sera obtained from over 400 patients.

2. Sera of normal individuals usually gave no titer or low titers but a few had high titers. The tuberculin-positive group had somewhat higher titers than the tuberculin-negative group.

\* Sera generously supplied by Dr. George Comstock.



3. In general those groups with active tuberculosis had higher titers than those with inactive disease but extremes of titers were found in both groups.

4. The average titers in active minimal and in moderately advanced tuberculosis were significantly higher than that of the normal group but many patients in the minimal group had low titers. The highest average titer was in the group with far advanced tuberculosis.

5. In a small group of patients with extrapulmonary tuberculosis the average titer was low and the range of titers was similar to that of the normal groups.

6. In a small group of patients with tuberculosis followed up over a long period of time some showed elevation of titers, some showed depression and others remained the same. There was no definite correlation of the effect of treatment with the trends of titers.

7. Sera of twenty-two patients with proven sarcoidosis yielded titers which were similar to the normal groups in their distribution and in their low average.

8. Following BCG vaccination of tuberculin-negative individuals there was an inconsistent response. Only 25 per cent showed a rise in titer in spite of all cases converting to tuberculin positivity.

9. Patients with syphilis, various pulmonary diseases and other miscellaneous diseases gave no indication of "false positives." The range of titers was similar to that of the normal groups.

10. With the old tuberculin antigen as used here the hemagglutination test for tuberculosis is by itself of limited clinical value. Elevation of titer is suggestive of tuberculosis in cases in which the differential diagnosis includes this disease. Absence of demonstrable circulating agglutinins does not rule out the presence of active tuberculosis.

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# Review

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## Behavior of the Myocardium in Health and Disease As Studied by Coronary Sinus Catheterization\*

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INVESTIGATION of hemodynamic problems has proceeded with such an impetus during the past twenty years that reports have become scattered in a multiplicity of journals. It is therefore appropriate from time to time to take stock of particular aspects. Within recent years intubation of the coronary sinus in dog and man has refocused interest in various aspects of myocardial activity.<sup>1-3</sup> The present paper discusses results obtained with this technic.

Although many writers during the past four centuries have accurately described the structure of the myocardium, it was Vieussens in the late seventeenth century who first described the structure of the left ventricle and the course of the coronary blood flow. In particular, for our present concern, he discussed the anatomy of the coronary sinus. In man this venous outflow remained an area of anatomic interest until a few years ago when during the passage of a cardiac catheter the coronary sinus was accidentally entered. Such a fortuitous occurrence stimulated interest in the possibility of intentional catheterization of the sinus and great cardiac vein for the purpose of obtaining further information of myocardial metabolism. Sufficient data have now been gathered with this technic in man to appraise what has been found by the procedure and to indicate the direction in which these results may influence future research.

The coronary sinus is difficult to catheterize in man mainly because of the variable and often prominent Eustachian ridge guarding the ostium of the sinus in the right auricle; however, once entered, the unusual anatomic configuration of the catheter, the marked desaturation of blood withdrawn, the low systolic pressure and lack of arrhythmias provide proof of entry. Thus it is possible with a minimum of disturbance to the patient to obtain samples of venous blood draining the myocardium. In order to obtain information of the composition of arterial blood entering the myocardium, blood from any systemic artery may be sampled. Any two such arterial and venous samples can provide useful information on the extraction of various metabolites by the area of myocardium drained by the coronary sinus. Work in this direction has been carried out by Goodale and his associates<sup>4</sup> who have estimated the extraction of pyruvate, lactate and glucose.

The estimation of coronary blood flow is more complicated but has been achieved by a modification of the nitrous oxide method of measuring cerebral blood flow.<sup>5</sup> The essence of the modification is that the desaturation rather than the saturation period is used in determining coronary blood flow.<sup>3</sup> This results in smooth nitrous oxide blood curves. Knowing the coronary blood flow and the arterial and coronary sinus oxygen content, the oxygen consump-

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tion for each 100 gm. of heart muscle may be calculated. Such calculations are valid unless coronary venous blood is contaminated with mixed venous blood. This is rare and can be suspected if the nitrous oxide content of coronary arterial blood and venous blood do not approach each other in the usual desaturation time of eight minutes.

As the coronary sinus drains primarily the left ventricular muscle, this article is limited to the activities either of the total left ventricular mass or the 100-gm. unit of left ventricular muscle. The present use of the term coronary flow therefore refers to the flow through the left ventricular muscle only.

What is the accuracy of this method? Visscher<sup>6</sup> has shown that coronary sinus blood does not represent true coronary mixed venous blood. This, however, does not detract from the accuracy of determinations made for a unit of left ventricular muscle since these determinations obtain only for that portion of the heart from which blood drains into the coronary sinus. This being so, reasonable observations can be made on the arterial supply of a standard weight of muscle fibers, and comparisons drawn between hearts *in vitro* and *in vivo*, especially with regard to the unit oxygen consumption in man and Starling's heart-lung preparation.

Unfortunately measurements for the total left ventricle are less accurate, involving as they do the assumption that coronary sinus blood is representative of all the blood which drains the left ventricle. Furthermore, calculations of total left ventricular weight from comparative tables, although reasonably accurate in *non*-hypertrophied hearts, must be grossly inaccurate in hypertrophied hearts. Therefore, approximations cannot be made for total left ventricular efficiency based on calculations of energy cost (energy provided by the consumption of oxygen) and cardiac work in hypertrophied hearts. It is clear, however, that if the maximal efficiency is low in a hypertrophied ventricle and the weight used in the calculation is for

a normal ventricle the loss of efficiency is significant. Estimation of total left ventricular efficiency is of further use when assessing the effects of drugs on the myocardium. The individual percentages of efficiency are immaterial but the changes in percentage are important.

These methods now make it possible to examine the cardiac pump itself rather than the effects of the pump's action in the form of cardiac output and pressure studies. The combination of all methods permits considerable insight into problems of basic hemodynamics and metabolic principles.

#### NORMAL MYOCARDIUM

In normal man at rest the myocardium extracts appreciably more oxygen than other organs so far tested, and the oxygen content of coronary venous blood varies from 4 to 7 volumes per cent, giving an average oxygen extraction of about 12 volumes per cent. The normal left ventricular coronary blood flow averages 65 cc. per minute for every 100 gm. of myocardium, and the oxygen consumption for the same unit of muscle weight averages 7.8 cc. per minute. Five to eight per cent of the cardiac output at rest is delivered to the heart. When compared with the percentage of cardiac output coursing through the kidney and liver the amount of blood perfusing the myocardium is small. In contrast to these organs the heart satisfies its oxygen requirements not by a large blood flow but by a high degree of oxygen extraction. In working skeletal muscle the normal venous oxygen content of 14 volumes per cent may drop to 7 or 8 volumes per cent, but work has to be exhaustive before levels are reached which are similar to those found in coronary venous blood in resting patients.<sup>7</sup>

It is of considerable interest that animal experimentation has shown a direct correlation between body weight, and consequently total heart weight, and left ventricular oxygen consumption and blood flow per 100 gm. of muscle. Small dogs have a relatively greater unit flow and oxygen



consumption than large dogs. This is presumably related to the proportionately larger surface area of small animals, increased metabolism of each unit of weight and therefore of each unit of tissue. These findings were obtained in unanesthetized dogs by Spencer<sup>8</sup> and lend support to the ability of the nitrous oxide method to record constant, reproducible physiologic events.

#### ABNORMAL MYOCARDIUM

*Anemia.* It has not yet been possible to obtain extensive experience of the behavior of the myocardium in patients suffering from chronic anemia. However, there has been sufficient consistency of results in patients catheterized to make some general remarks.

When blood with an inadequate oxygen content perfuses tissues, the usual tissue reaction is to extract oxygen to lower venous levels and in this the myocardium is no exception.<sup>9</sup> In two patients with  $8\frac{1}{2}$  gm. of hemoglobin the coronary sinus blood contained only 1.6 volumes per cent of oxygen. Increased oxygen extraction is one adaptive mechanism, but the vascular response in the form of increased blood flow is of great if not greater importance. It is now well known that in severe chronic anemia the cardiac output is greatly augmented<sup>10</sup> producing the so-called hyperkinetic state. The coronary flow shares in this augmentation and is probably proportionately increased. Two factors which may operate under these circumstances are: (1) anoxia which in experimental conditions in intact hearts acts as a potent vasodilator,<sup>11</sup> and (2) also in intact hearts *in vitro* there is a correlation between cardiac output and coronary flow which is independent of variation in systemic arterial pressure.<sup>12</sup> In one patient with chronic anemia of severe degree (hemoglobin of  $4\frac{1}{2}$  gm.) studied in this laboratory the resting cardiac output was 8 L. per minute and the unit coronary flow more than trebled to 300 cc. per minute. The arteriovenous coronary oxygen difference was only 4 volumes per cent. At rest the

cardiac oxygen consumption per unit of myocardium was normal. There is, therefore, evidence that the coronary blood flow is increased in anemia. However, experience in this laboratory indicates that the flow may not always be adequate to meet the metabolic demands of the myocardium in these circumstances.

As the oxygen tension of coronary venous blood is low in anemic patients so also must the myocardial oxygen tension be low. The observations of Blumgart and Zoll<sup>13</sup> that in the pig chronic anemia favors the production of intercoronary arterial anastomoses are most interesting. It may be that the low tissue oxygen tension is the stimulus for alteration of the anatomic vascular pattern. Work on the effect of reduced oxygen tension on capillary growth might well yield important results.

It must be stressed that this discussion is limited to resting conditions but there is sufficient clinical and pathologic evidence to suggest that anemic patients on effort may not have a sufficient myocardial oxygen supply. Angina pectoris, especially when it occurs in young women with anemia, is usually not associated with any coronary arterial disease and there is complete relief from pain when normal hemoglobin is attained.

*Thyrotoxicosis.* In the hyperkinetic state resulting from thyrotoxicosis the oxidative metabolism of the heart per unit weight is, surprisingly enough, normal.<sup>3</sup> This observation agrees with that of Dock and his associates.<sup>14</sup> In this respect the hypertrophied thyrotoxic heart is similar to the hypertrophied heart in essential hypertension. Thyroxin apparently does not increase the unit oxygen consumption of the myocardium but only the total left ventricular oxygen consumption by virtue of increased myocardial mass. It may be inferred, that thyroxin has no effect on cardiac metabolism. However, there is evidence to suggest that thyroxin produces auricular fibrillation before congestive failure occurs.<sup>16</sup> This action, the production of arrhythmias without alteration of myocardial oxidative



metabolism, is in some respects similar to that of the cardiac glycosides.

*Hypertension and Aortic Valvular Disease.* The cardiac hypertrophy resulting from essential hypertension is not accompanied with any significant increase in coronary blood flow or oxygen consumption for every 100 gm. of muscle and the arteriovenous oxygen difference is normal. The total ventricular oxygen consumption and coronary flow must be increased but cannot be assessed in hypertrophied hearts. Therefore, a heart which has been working against increased resistance for a period of time adapts itself not by altering the vascular supply to individual fibers but by a total increased flow. This fits in with the findings of Roberts and Wearn<sup>17</sup> that there is no alteration in capillary supply to hypertrophied fibers. It does not mean, of course, that because a hypertrophied fiber uses a normal amount of oxygen it is not at a disadvantage. Hill<sup>18</sup> has found that the rate of oxygen diffusion through tissues varies as the space of distance increases, which suggests that if cardiac fibers are much hypertrophied and the oxygen tension unchanged they will suffer from relative anoxia.<sup>19</sup>

The normal coronary flow per unit of myocardium in hypertension implies that the coronary vascular resistance shares in the general increased arterial resistance, and measurements prove this to be so. A similar state of affairs has been found in the brain where in hypertension the resistance may be raised up to 88 per cent while the flow and oxygen consumption remain normal.<sup>20</sup>

It might well be argued that when measuring coronary blood flow by this method scarred areas of myocardium due to infarction or diffuse fibrosis will not take up oxygen or other gases in the same way as normal muscle and therefore, that the estimated oxygen consumption and flow are incorrect. This should be suspected if the arterial and venous nitrous oxide curves do not equilibrate in eight minutes. In a single patient with a cardiac output of 8 L. per minute, who had both anemia and electro-

cardiographic evidence of myocardial ischemia, the oxygen extraction and the oxygen consumption per 100 gm. were reduced more than in patients with a similar degree of anemia.<sup>3</sup> This suggests that a considerable amount of scar tissue must have been perfused. Further work along these lines is desirable, particularly in elucidating the clinical problem of combined angina pectoris and hypertension. Is the angina existing in hypertensive patients the result of coronary arteriosclerosis or is it a relative deficiency on exercise, the oxygen demand of the hypertrophied ventricle exceeding the supply? If the angina is a result solely of hypertrophy, there should be considerable benefit from prolonged hypotensive treatment and consequent decrease in hypertrophy; but if it is due to arteriosclerosis, a lowering of blood pressure may predispose to coronary thrombosis. Similar problems arise in patients with cardiac hypertrophy due to other causes. For example, in aortic stenosis the coronary flow and cardiac oxygen consumption per unit weight are normal at rest, but even minor increases in cardiac work call for increased oxygen supply which cannot be met because of the limited ability to increase cardiac output. As a result angina pectoris frequently results on minor exertion.

The alteration in coronary hemodynamics in coarctation of the aorta differs from the hemodynamics of essential hypertension.<sup>3</sup> In coarctation the coronary arteriovenous oxygen difference, the left ventricular coronary flow, and oxygen consumption per 100 gm. are all increased. The fact that the flow is greater in younger individuals with relatively smaller hearts does not entirely explain the contrast, for it is also greater in older patients although not to the same degree. The only explanation that can be offered is that there is no generalized elevation of the peripheral vascular resistance, and the resistance varies in different locations.<sup>21</sup> In a small series of patients the coronary resistance in coarctation was within the range of normal and less than that in essential hypertension.

*Myocardium in Cardiac Failure.* In heart failure due to arteriosclerotic heart disease, mitral stenosis and insufficiency or aortic valvular disease, the coronary blood flow per unit myocardium is normal, the oxygen extraction a little above normal, and consequently the oxygen consumption slightly increased. All patients with mitral disease who were studied had radiologic evidence of enlarged left ventricles. In such patients, of course, present day methods do not give a satisfactory estimate of cardiac output but merely of that fraction of blood which passes into the aorta (systemic flow). In some patients the measured cardiac output was low and, with the aforementioned proviso, probably absolutely so. The low cardiac output resulted in a diminution in the work of the heart and it was this factor which was responsible for the decrease in myocardial efficiency.

Increase in over-all resistance in cardiac failure has been found.<sup>22</sup> In particular the brain<sup>20</sup> and kidney<sup>23</sup> share in this increase. By contrast, calculations from data obtained in this laboratory show that the vascular coronary resistance in cardiac failure is normal.<sup>24</sup>

What then are the special features of the failing myocardium? In the brain the increased oxygen extraction is not commensurate with the lowered blood flow and Scheinberg suggests that there may be difficulty in extracting oxygen when the venous tension falls.<sup>20</sup> In cardiac failure the liver and kidneys extract more oxygen as the flow decreases.<sup>25</sup> The heart not only maintains the coronary flow until failure becomes severe but also extracts oxygen to such a degree that the coronary sinus blood contains less than 3 volumes per cent.<sup>3</sup> The coefficient of oxygen utilization of the myocardium is normally about 60 per cent and can increase in failure to almost 90 per cent. The per cent oxygen utilization of the brain,<sup>20</sup> kidney,<sup>25</sup> and liver<sup>26</sup> also increases in cardiac failure but not as strikingly as that of heart muscle.

The most important step in the understanding of the mechanism of myocardial

failure is the realization that oxygen consumption per unit of myocardium is normal or only slightly increased. There appears to be no failure in the oxidative energy production. In support of these findings Goodale<sup>4</sup> has shown that the extraction of glucose by the normal heart is considerable, and that glucose, pyruvate and lactate metabolism appears to be normal in the failing heart. This suggests that the carbohydrate metabolism of the failing heart is essentially normal. For this reason Goodale's suggestion that "liberal glucose administration may benefit the failing heart" is well taken.<sup>4</sup> The old advice that enthusiastic insulin therapy in diabetes complicated by failure is to be avoided now has some backing because the failing heart has not lost its ability to utilize this form of energy.

#### EFFECT OF CARDIAC GLYCOSIDES ON THE MYOCARDIUM

Considerable time has been devoted by many investigators to the action of such drugs as digitalis and strophanthus preparations on the heart. They have been mainly concerned with the effect of the drugs on the venous, intracardiac, pulmonary and systemic pressures, the arterio-mixed venous oxygen difference and the cardiac output. It is agreed that in the normal subject in experiments extending over one to two hours the cardiac output falls and the systemic arterial pressure remains normal or rises a little. It is also agreed that in the majority of varieties of cardiac failure the output and stroke volume increase and the venous pressure and peripheral resistance fall following administration of cardiac glycosides.<sup>27-29</sup> If the pulmonary pressure is initially raised, it usually falls after medication. There is, however, considerable discussion as to how an increased output is achieved. It is possible that at least digoxin has some action on venomotor tone,<sup>29</sup> but it is highly probable that both digoxin and strophanthus preparations have a direct myocardial action. What that action is remains unknown, but coronary sinus catheterization has offered certain leads.



Strophanthus K and strophosid when given in doses of 0.5 mg. to normal individuals lower cardiac output but do not alter the coronary blood flow per 100 gm. of muscle or the coronary arteriovenous oxygen difference. Consequently the cardiac oxygen consumption remains the same. The heart is therefore doing less work but is using the same amount of oxygen and the loss of efficiency is sometimes great.<sup>30</sup>

In the failing heart, as already mentioned, the coronary unit blood flow is normal and the coronary arteriovenous difference slightly increased, but the cardiac output is low. Strophanthus preparations increase the cardiac output but do not significantly alter the coronary flow or arteriovenous oxygen difference. The heart becomes *more* efficient, in one instance by as much as 50 per cent.<sup>30</sup> Thus the heart does not gain in efficiency by decreasing energy consumption. The conclusion is that it develops greater facility either in transferring oxidative energy into mechanical work or in the utilization of energy.

Throughout these changes, both in the normal and failing heart, the coronary resistance is not materially altered by strophanthus preparations and it is not possible to evoke any specific action of strophanthus on the coronary bed.<sup>30</sup>

#### MYOCARDIAL FUNCTION IN VITRO AND IN VIVO

In view of all this evidence obtained by coronary sinus catheterization it is worth while to review and contrast the state of affairs in isolated heart preparations and in man. In Starling's classic heart-lung preparation he found that "increased liberation of energy results from the contraction of the heart muscle when there is an increased diastolic volume of the heart and vice-versa."<sup>31</sup> Also, according to Starling and Visscher,<sup>32</sup> "the oxygen consumption of the isolated heart maintained under constant chemical and temperature conditions is determined by its diastolic volume and therefore by the initial length of its muscular fibers." In the non-failing heart

*in vitro*, then, unit oxygen consumption will alter both with the diastolic volume and the work of the heart. In the failing heart *in vitro* unit oxygen consumption will increase with the diastolic volume but the work will decrease as the failure progresses. Thus the heart *in vitro* becomes more efficient as the load increases; but as failure develops, the oxygen consumption outstrips the work and the efficiency declines. Coronary sinus catheterization has revealed differences between the normal and failing heart both *in vitro* and *in vivo*.

When for any reason the left ventricular load is increased without evidence of failure, the response of the heart is to hypertrophy; but as already stressed the unit oxygen consumption is not raised. This is in contrast to the heart-lung preparation when acute increases in load are added. There the load is met by increased oxygen consumption per unit of fiber. The difference lies in the fact that in man chronic loads are met by an increase in over-all oxygen consumption but *not* in oxygen consumption per 100 gm. of muscle. Hypertrophied fibers weigh more, weight for weight, but consume normal amounts of oxygen.

In cardiac failure in man the unit oxygen consumption is normal or slightly elevated although there is radiologic evidence of left ventricular enlargement. In Starling and Visscher's preparations acute cardiac failure was always accompanied with increased unit oxygen consumption which they regarded as due to increased fiber length. In patients with cardiac failure the left ventricular fiber length presumably is increased and therefore the left ventricular energy consumption per unit weight should be increased commensurately. This is not the case; therefore, doubt must be cast on the application of Starling's hypothesis in the types of cardiac failure so far studied. This by no means invalidates the hypothesis that an acute increase in diastolic volume in man may lead to an increase in oxygen consumption per unit weight and increase in cardiac output. It may well be that the biophysical and biochemical events are different when



the myocardium is exposed to acute and chronic increases in load.

The cardiac efficiency of normal left ventricular muscle is about 23 per cent. As already mentioned it is impossible to calculate accurately the efficiency of the failing ventricle because of the difficulty in estimating its weight, but by calculating efficiency from normal heart weight maximal values are obtained. These values are lowered in patients with congestive failure, the efficiency dropping to between 10 and 17 per cent.<sup>3,30</sup> A similar type of observation was made by Moe and Visscher<sup>33</sup> *in vitro* when they reduced the cardiac output but kept the diastolic volume and hence oxygen consumption the same.

What then is the essential disability of the failing human heart? The output is lowered and the efficiency decreased and yet the oxygen consumption per 100 gm. of myocardium is only slightly elevated. Katz<sup>34</sup> found in *in vitro* experiments that the disability is a failure of total energy liberation for a given fiber length. Visscher<sup>35</sup> believes that it is a reduction of the proportion of total energy expended in performing useful work (failure of mechanical efficiency). We side with the latter although for different reasons; the question of raised or normal oxygen consumption. As far as the human heart is concerned it seems that the heart is unable to transfer oxidative energy into useful work.

Investigative effort should now be directed to a comparison of the enzymatic reactions of the normal and diseased myocardium. Knowledge of these processes in normal skeletal muscle is very considerable.<sup>36</sup> Horváth and his colleagues<sup>37</sup> have already recorded experiments on the effect of cardiac glycosides on the polymerization of actin, and Cameron<sup>38</sup> has recently produced evidence that these drugs may act on or in the vicinity of the contractile mechanism of the muscle cell. The results so far obtained from coronary sinus catheterization point to the importance of the application of these studies to the problem of myocardial failure.

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# Seminars on Pulmonary Physiology

## Influence of Chronic Pulmonary Disease on the Heart and Circulation\*

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EXTENSIVE investigations in the past two decades have afforded a better understanding of the various forms of abnormal pulmonary physiology which may occur in chronic lung disease. These forms of pulmonary insufficiency have been identified by means of pulmonary function studies and the patterns specific to each of a wide variety of diseases are now fairly well recognized. As expected, the patterns of pulmonary dysfunction vary considerably from one disease process to another. Furthermore, the respiratory abnormalities associated with a single disease may alter considerably during the evolutionary phases of the illness. It has also been found that the sequelae initiated by one type of pulmonary dysfunction may differ widely from those of another. With such evident diversity of pulmonary function the effects upon the circulation might also be variable. It therefore seems wise to examine the heart and circulation systematically in all varieties of pulmonary disease.

Several attempts have been made in the past to study the effects of chronic lung disease upon the circulation. Taquini and his group,<sup>1,2</sup> examining patients with fibrosis and emphysema, have emphasized the finding of a normal cardiac output (using the acetylene method) unless cardiac insufficiency exists. In the latter event the output is low. McMichael<sup>3,4</sup> has stated that cases of cor pulmonale in failure, which he called "emphysema heart," may have a high cardiac output, and this was confirmed by Richards.<sup>5</sup> The catheterization technic has permitted measurements of right heart pressures in chronic lung disease<sup>6-8</sup> while the relationship between

blood flow and pulmonary hypertension has been clearly demonstrated by means of exercise studies.<sup>9,10</sup> However, there has been no report of extensive concurrent studies of pulmonary and cardiac function. It may well be that the disagreements concerning the influence of chronic pulmonary disease upon the circulation are due to the fact that the various investigators studying circulatory function are not reporting upon patients with the same type of pulmonary disease.

If the confused picture which now exists concerning the circulatory complications of pulmonary disease is to be clarified, a systematic analysis of pulmonary and circulatory function must be initiated. To cover adequately the entire subject of the circulatory effects of chronic pulmonary disease will require many years of observation over a wide range of patient material. This paper represents only an initial report since it has not been possible to date to accumulate sufficient data on many aspects of the problem. The available material is nevertheless presented in order to outline the circulatory complications in certain specific forms of pulmonary dysfunction and to demonstrate, whenever possible, the pathogenesis of these complications. A better understanding of chronic cor pulmonale may thus be achieved. In some instances incomplete data permit only the formulation of a working hypothesis which may be subject to revision in the light of future investigations.

The discussion of pulmonary function will be less detailed in this report than that of the circulatory performance. It cannot, however,

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TABLE I  
PHYSICAL CHARACTERISTICS AND DIAGNOSES IN FORTY-EIGHT CASES  
OF CHRONIC PULMONARY DISEASE

Case No.	Diagnosis	Sex	Age (yr.)	Wt. (kg.)	BSA (M <sup>2</sup> )	Comments
168	Chr. pul. emphysema (i)	M	48	69	1.92	None
551	Chr. pul. emphysema (i)	M	60	63	1.69	None
219	Chr. pul. emphysema (i)	M	50	61	1.78	None
142	Chr. pul. emphysema (i)	F	62	45	1.36	None
	Asth. bronchitis					
298	Chr. pul. emphysema (i)	M	25	66	1.84	None
	Air cysts of lungs					
541	Chr. pul. emphysema (i)	M	62	55	1.61	None
	Bron. ca. RUL.					
	Pul. hypertension					
173	Chr. pul. emphysema (ii)	M	44	53	1.56	None
	Pul. hypertension					
95	Chr. pul. emphysema (iii)	M	40	53	1.54	None
	Pul. hypertension					
82	Chr. pul. emphysema (iii)	M	58	47	1.50	None
	Pul. hypertension					
489	*Chr. pul. emphysema (iii)	M	72	56	1.64	No failure
	Pul. hypertension; later developed chronic cor pulmonale		73	52	1.58	Recovered from failure; digitalized
474	Chr. pul. emphysema (iii)	F	23	41	1.37	None
	Bronchial asthma					
	Pul. hypertension					
	Dilated pul. artery					
537	Chr. pul. emphysema (iii)	F	52	82	1.88	None
	Bronchial asthma					
	Pul. hypertension					
582	Chr. pul. emphysema (iv)	M	46	52	1.61	Digitalized
	Chronic cor pulmonale					
	EH. NSR. II B					
532	Chr. pul. emphysema (iv)	M	50	54	1.55	No digitalis
	Chronic cor pulmonale					
	EH. NSR. II B					
468	Chr. pul. emphysema (iv)	M	48	64	1.63	No digitalis
	Chronic cor pulmonale					
	EH. dilated pul. artery					
	NSR. II B					
98	Chr. pul. emphysema (iv)	M	62	57	1.72	Digitalized
	Chronic cor pulmonale					
	EH. NSR. II B					
452	Chr. pul. emphysema (iv)	M	48	46	1.48	No digitalis
	Chronic cor pulmonale					
	EH. NSR. II B					
529	Chr. pul. emphysema (iv)	M	48	50	1.54	Recovering from failure; no digitalis
	Bronchial asthma					
	Chronic cor pulmonale					
	EH. NST. Gallop rhythm III C					

BSA = Body surface area in square meters

Numerals i, ii, iii, iv following diagnosis of pulmonary emphysema refer to the classification of Baldwin et al.<sup>16</sup>

Numerals and letters following cardiac diagnoses indicate the functional and therapeutic classification according to accepted criteria.<sup>31</sup>

Chr. pul. emphysema = Chronic pulmonary emphysema

Asth. bronchitis = asthmatic bronchitis

Bron. ca. RUL. = Bronchogenic carcinoma of right upper lobe

Pul. hypertension = Pulmonary hypertension

Dilated pul. artery = Dilated pulmonary artery

EH = Enlarged heart

NSR = Normal sinus rhythm

NST = Normal sinus tachycardia

CHF = Congestive heart failure

SA = Sinus arrhythmia

Int. obst. pul. emp. = Intermittant obstructive pulmonary emphysema

Gen. arteriosclerosis = Generalized arteriosclerosis

Chr. pul. tbc. = Chronic pulmonary tuberculosis

Pul. vasc. disease = Pulmonary vascular disease

\* Diagnoses confirmed by necropsy.

TABLE I (Continued)

Case No.	Diagnosis	Sex	Age (yr.)	Wt. (kg.)	BSA (M <sup>2</sup> )	Comments
507	Int. obst. pul. emp. (iv) Bronchial asthma Chronic cor pulmonale EH. NST. (uB and ivD)	M	38	46	1.47	Recovered from failure; digitalized
471	Int. obst. pul. emp. (iv) Bronchial asthma Chronic cor pulmonale EH. NSR. (uB and ivD)	F	55	46 55	1.46 1.58	In congestive failure; digitalized Recovered from failure; digitalized
528	Chr. pul. emphysema (iv) Chronic cor pulmonale EH. NSR. and NST. (uB and ivD)	M	52	63 54	1.65 1.54	In congestive failure; no digitalis Recovered from failure; digitalized
514	* Chr. pul. emphysema (iv) Bronchiectasis Chronic cor pulmonale EH. NSR. (uB and ivD)	M	60	60 51	1.61 1.55	In congestive failure; no digitalis Recovered from failure; digitalized
127	* Chr. pul. emphysema (iv) Chronic cor pulmonale EH. NSR. CHF. ivD	M	64	60 70	1.62 1.80	In congestive failure; no digitalis In congestive failure; digitalized
132	Chr. pul. emphysema (iv) Chronic cor pulmonale EH. dilated pul. artery, NST. CHF. ivD	M	58	58	1.64	In congestive failure; digitalized
467	Chr. pul. emphysema Silicosis, fine nodular Pul. hypertension Gen. arteriosclerosis	M	65	75	1.90	None
430	Chr. pul. emphysema Silico-tuberculosis, nodular Pul. hypertension	M	59	61	1.66	None
139	Chr. pul. emphysema Silicosis, conglomerate, apical Pul. hypertension	M	59	53	1.64	None
149	Chr. pul. emphysema Silicosis, conglomerate, apical Pul. hypertension	M	38	42	1.44	None
423	Chr. pul. emphysema Silicosis, conglomerate, apical Pul. hypertension	M	46	53	1.55	None
487	Chr. pul. emphysema Silicosis, conglomerate Chronic cor pulmonale EH. SA. uB	M	54	68	1.77	Recovered from failure; no digitalis
465	Chr. pul. emphysema Silicosis, fine nodular Chronic cor pulmonale NSR. uB	M	65	57	1.60	Recovered from failure; no digitalis
496	Chr. pul. emphysema Silico-tuberculosis, nodular, apical Chronic cor pulmonale EH. NSR. (uB and ivD)	M	55	52 71	1.57 1.78	Recovered from failure; digitalized In congestive failure; no digitalis
458	Silicosis, large nodular Pul. hypertension	M	66	67	1.74	None

BSA = Body surface area in square meters

Numerals i, ii, iii, iv following diagnosis of pulmonary emphysema refer to the classification of Baldwin et al.<sup>18</sup>Numerals and letters following cardiac diagnoses indicate the functional and therapeutic classification according to accepted criteria.<sup>21</sup>

Chr. pul. emphysema = Chronic pulmonary emphysema

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\* Diagnoses confirmed by necropsy.

TABLE I (Continued)

Case No.	Diagnosis	Sex	Age (yr.)	Wt. (kg.)	BSA (M <sup>2</sup> )	Comments
101	Silicosis, fine nodular Chronic cor pulmonale EH. dilated pul. artery NSR. (III C and IV D)	M	52	55	1.63	In congestive failure
				55	1.62	In congestive failure, improved; on digitalis
				55	1.63	In congestive failure; digitalis toxicity with coupling
521	Scleroderma of skin and lungs Pul. hypertension Dilated pul. artery	F	22	47	1.42	None
501	Granulomas of lungs Beryllium exposure	F	34	54	1.55	None
534	* Granulomas of lungs Beryllium exposure	M	66	55	1.64	None
515	* Infiltration of lungs and granulomas of lymph nodes, unknown type Pul. hypertension	F	47	54	1.55	None
548	Granulomas of lungs and lymph nodes Pul. hypertension	M	17	45	1.47	None
476	Subacute bilateral infiltration of the lungs Pul. hypertension	M	29	61	1.69	None
483	* Granuloma of lungs; Boeck's sarcoid Intermittent pul. hypertension	F	47	60	1.67	None
413	Chr. diffuse reticular fibrosis of lungs Pul. hypertension	F	60	48	1.68	None
464	Chr. diffuse reticular fibrosis of lungs	M	43	46	1.47	None
584	Chr. diffuse reticular fibrosis of lungs Chronic cor pulmonale EH. NSR. CHF. III C	F	64	46	1.47	In congestive failure; digitalized
344	* Multiple pul. emboli Thrombosis left pul. artery Chronic cor pulmonale EH. NST. CHF. IV D	F	41	47	1.39 1.42	In congestive failure; digitalized In congestive failure; digitalized
526	* Chr. pul. Emphysema Chr. pul. tbc. III C Multiple pul. emboli Chronic cor pulmonale EH. NST. (II B and IV D)	F	35	37	1.26	Recovered from failure; digitalized
				40	1.30	In congestive failure; no digitalis
327	? Pul. vasc. disease Chronic cor pulmonale EH. dilated pul. artery NST. CHF. IV D	F	43	51	1.43	In congestive failure; digitalized
300	? Pul. vasc. disease Chronic cor pulmonale EH. dilated pul. artery NSR. gallop rhythm CHF. III C	M	40	68	1.77	In congestive failure; digitalized

BSA = Body surface area in square meters  
 Numerals I, II, III, IV following diagnosis of pulmonary emphysema refer to the classification of Baldwin et al.<sup>16</sup>  
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 Pul. hypertension = Pulmonary hypertension  
 Dilated pul. artery = Dilated pulmonary artery

EH = Enlarged heart  
 NSR = Normal sinus rhythm  
 NST = Normal sinus tachycardia  
 CHF = Congestive heart failure  
 SA = Sinus arrhythmia  
 Int. obst. pul. emp. = Intermittant obstructive pulmonary emphysema  
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 Chr. pul. tbc. = Chronic pulmonary tuberculosis  
 Pul. vasc. disease = Pulmonary vascular disease  
 \* Diagnoses confirmed by necropsy.



be overemphasized that a thorough understanding of pulmonary function is crucial to appreciation of the effects of its derangements upon the circulatory function.

#### MATERIAL FOR STUDY

Studies of both pulmonary and cardiac function were made in forty-eight cases of chronic pulmonary disease. The individual diagnoses can be found in Table I. This material, although not specifically selective, represents nonetheless a special group since the majority of patients had either respiratory or cardiac symptoms or both and were therefore admitted to the medical or chest services in a large municipal hospital. Furthermore, with few exceptions the average age of these patients was fifty, with a range of seventeen to seventy-three years. This results from the nature of the population in general admitted to the hospital. Finally, patients with heart disease other than cor pulmonale and those with renal or hepatic disease were specifically excluded. Thus an attempt was made to secure only those patients with chronic lung disease and its circulatory complications. They were chosen from a larger group because the studies of cardiopulmonary function were extensive and definitive. Studies of such patients have been in progress over a number of years.

In the early period when technics of examination were evolving, many cases were incompletely assessed and hence are not included in this report. Interest has often centered around certain specific diseases, such as emphysema and diffusion fibrosis, thus artificially increasing the number of such cases studied. On the other hand, there has not been as yet a good opportunity to study silicosis adequately and this creates a considerable gap in our experience. Silicosis in patients reported was discovered incidentally and they were not referred to the hospital for appraisal of this type of pneumoconiosis. Studies of cardiopulmonary function in patients with surgical chest problems, such as pneumonectomy, have been reported separately.<sup>11</sup>

#### METHODS

The patients included in this report had determinations made of lung volumes, maximum breathing capacity and respiratory gas exchange by methods previously published.<sup>12</sup> Circulatory measurements were made by means of cardiac catheterization and included cardiac output and index, peripheral arterial, pulmonary arterial

and right ventricular pressures and blood volume.

#### RESULTS

The patients are grouped primarily according to the nature and severity of the pulmonary disease. The largest group are cases with chronic pulmonary emphysema alone. Smaller groups include cases with silicosis and emphysema, silicosis alone, diffusion fibrosis,<sup>13,14</sup> multiple pulmonary emboli and certain cases of unknown pulmonary disease.

*Chronic Pulmonary Emphysema.* The diagnosis of chronic pulmonary emphysema in these twenty-four patients was made according to criteria previously published.<sup>15</sup> The severity of the disease was judged by the degree of arterial blood unsaturation at rest and after the standard exercise test.<sup>12,15</sup> Thus two criteria were used in classifying these patients into a number of groups, namely, the degree of arterial blood anoxia and a history of cardiac failure.

As can be seen in Table II A patients classed as mild emphysema had either normal arterial blood oxygen saturation (98 to 94 per cent) or only a slight degree of unsaturation (93 to 90 per cent) at rest and did not decrease their saturation after exercise. Except for one patient (No. 142) there was no elevation of the CO<sub>2</sub> tension in the arterial blood. The patients classed as severe emphysema (Table II B), however, had arterial blood oxygen unsaturation at rest to a greater or lesser degree and showed marked unsaturation after exercise. In addition, carbon dioxide retention was usually present. None of the patients in group A or B had evidence of cardiac failure. The remaining twelve patients (groups C, D and E in Table II) had emphysema and chronic cor pulmonale and were studied in various states of cardiac compensation. One of the patients in group B (No. 489) subsequently went into cardiac failure and following recovery from failure he was restudied and appears in group C. As can be seen in Table II the four patients in group D, first studied in failure, also appear in group C after recovery from failure. The two patients in group E could never be restored to compensation and died within a few months of these studies.

The patients with mild emphysema and only minimal arterial blood anoxia had no demonstrable alteration of the circulation at rest. On the other hand, in patients with emphysema severe enough to cause either arterial blood

TABLE II  
CARDIOPULMONARY FUNCTION IN TWENTY-FOUR PATIENTS  
WITH CHRONIC PULMONARY EMPHYSEMA

Case No.	Lung Volumes		M.B.C. (% Pred.)	Arterial Blood				Oxygen Consump- tion (cc./min./ M <sup>2</sup> BSA)	Cardiac Output (L./min.)	Cardiac Index (L./min./ M <sup>2</sup> BSA)	Heart Rate (Beats per min.)	Peripheral Artery Pressure (mm. Hg)		Pulmonary Artery Pressure (mm. Hg)		Right Ventricle Pressure (mm. Hg) d	Blood Volume		Hematocrit (%)														
				Cap. (Vol. %)	Oxygen							s/d	m	s/d	m		TBV	PV															
	T.C. (% Pred.)	RA TC × 100			Saturation %		pCO <sub>2</sub> (mm. Hg)																										
		R			E																												
Normal	100	25	100	20.0	97	79	39		5.5	3.12	80	120/70	90	30/10	15		2900	1600	45														
(A) Emphysema, Mild																																	
168 G. J.	111	40	58	16.9	98	96	38	128	5.12	2.67	56	142/74	99	30/..	..	1	2860	1720	40														
551 S. A.	130	48	43	17.2	93	94	41	120	4.51	2.67	75	139/77	100	24/10	15	1	2385	1428	43														
219 W. K.	130	47	39	19.1	93	96	40	120	6.30	3.54	98	.....	74	23/..	..	2	....	....	..														
142 S. D.	108	59	43	18.1	90	93	45	135	4.60	3.38	80	106/64	80	26/..	..	4	2380	1490	37														
298 W. Z.	134	41	48	19.3	93	92	37	160	6.68	3.63	64	107/58	81	24/7	12	3	3430	1930	34														
541 D. McG.	142	51	56	16.9	93	..	40	149	5.71	3.55	75	136/66	96	30/9	19	2	2803	1687	39														
Average	126	48	48	17.9	93	94	40	135	5.50	3.24	75	126/68	89	26/9	15	2	2770	1650	39														
(B) Emphysema, Severe																																	
173 S. A.	124	59	27	21.9	93	46	39	156	4.44	2.85	66	137/82	103	39/..	..	2	2900	1420	51														
95 S. D.	92	63	23	18.8	86	..	55	155	5.83	3.78	78	124/60	84	41/..	..	0	3080	1635	47														
82 J. B.	117	64	..	19.9	81	..	53	138	5.45	3.63	72	166/88	118	44/..	2	2	3270	1665	49														
489 J. McC.	102	57	33	20.0	94	67	52	148	5.65	3.45	85	164/85	113	43/10	25	2	3740	1860	50														
474 H. W.	110	73	22	18.3	81	49	54	140	6.20	4.53	85	101/63	78	37/15	26	2	3080	1585	49														
537 M. N.	53	48	36	20.4	79	..	52	149	5.96	3.17	78	118/49	75	34/14	23	4	3340	1665	50														
Average	98	61	28	19.9	86	54	51	148	5.60	3.57	77	135/71	95	40/13	25	2	3240	1640	49														

(C) Emphysema and Chronic Cor Pulmonale—Recently in Cardiac Failure

582 W. B.	132	42	71	21.6	90	85	38	138	3.84	2.39	56	124/76	98	26/8	16	2	3907	1703	56
489 J. McC.	95	64	22	20.4	83	..	52	150	4.70	2.99	71	121/61	78	45/17	25	0	3945	1832	54
532 J. McC.	86	51	28	20.8	85	..	45	141	5.62	3.62	95	91/63	75	38/13	26	2	3550	1525	57
A. P.	134	49	21	20.0	83	75	50	154	5.84	3.58	83	109/68	83	35/17	23	0	3650	1595	56
468 L. P.	72	45	40	20.2	86	..	52	146	5.46	3.17	68	140/76	97	49/..	..	3	3640	1856	49
S. K.	125	77	31	18.7	90	62	49	138	4.76	3.28	96	119/74	95	39/..	..	1	3630	1620	55
452 T. D.	64	54	23	20.3	63	..	58	168	4.62	3.00	115	121/84	99	76/32	46	6	2909	1456	49
529 M. C.	58	23	35	17.9	84	..	62	156	6.80	4.63	106	112/72	84	43/21	30	..	3970	2080	48
A. Y.	98	36	70	18.2	79	66	40	140	6.00	3.80	77	142/79	106	33/15	21	2	3620	1860	48
471 A. D.	118	51	53	18.9	90	..	47	136	5.12	3.33	93	109/62	80	26/11	15	0	3080	1630	47
528 B. B.	86	47	77	17.8	85	76	52	146	5.98	3.91	75	95/53	70	32/12	21	1	4035	2100	48
514 J. B.	97	49	43	19.6	81	73	50	147	5.35	3.44	84	117/70	88	40/16	25	2	3630	1750	52
Average																			

(D) Emphysema and Chronic Cor Pulmonale—in Cardiac Failure (Reversible)

507 A. Y.	61	42	22	23.7	53	..	71	171	5.95	4.08	111	120/77	91	68/37	47	9	5360	1638	70
471 A. D.	112	42	51	20.5	60	..	53	170	10.00	6.06	97	140/75	103	63/29	44	10	6070	2040	66
528 B. B.	73	59	23	21.3	61	..	72	160	7.14	4.43	109	103/69	82	72/36	49	15	5250	1610	69
514 J. B.	...	..	..	15.7	55	..	64	157	6.54	4.04	100	114/78	82	82/42	55	17	4125	1896	54
Average	82	48	32	20.3	58	..	65	165	7.40	4.65	104	119/75	90	71/36	49	13	5180	1790	65

(E) Emphysema and Chronic Cor Pulmonale—in Cardiac Failure (Irreversible)

127 L. C.	66	65	19	17.8	84	..	62	153	5.50	3.05	104	157/74	105	.....	..	9*	3820	1750	54
132 S. S.	105	73	13	26.6	66	..	60	152	4.24	2.59	108	133/64	89	.....	..	14*	4730	1580	67

\* End diastolic pressure measured on right auricular curves.

T.C. = Total capacity

% Pred. = Per cent of predicted

RA X 100 = Ratio of residual air to total capacity

TC

M. B. C. = Maximum breathing capacity

Cap. = Capacity

Sat. = Saturation

R = Resting basal state

E = After the standard exercise of 30 steps in one minute

s = systolic

d = diastolic

m = mean

TBV = Total blood volume

PV = Plasma volume



oxygen saturation of less than 90 per cent at rest or whose arterial blood oxygen saturation decreased markedly after exercise, it is apparent that in addition to slight elevation of the resting cardiac output, total blood volume and hematocrit there is moderate pulmonary artery hyper-

pulmonary hypertension. The diastolic pressure in the right ventricle was markedly elevated, a manifestation of right heart failure, and the cardiac output was high. It should be especially noted that in this form of polycythemia although the red cells are increased in number they are

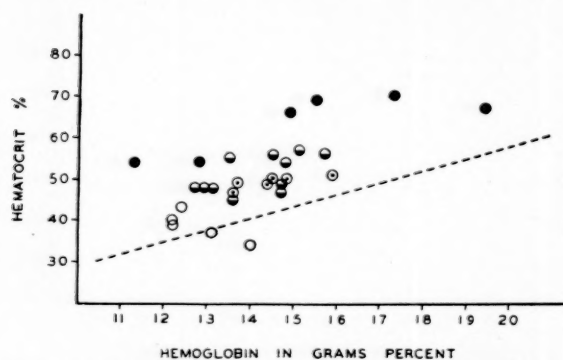


FIG. 1. Relation between volume and hemoglobin content of red blood cells in chronic pulmonary emphysema. The normal relationship between hematocrit and hemoglobin concentration in gram per 100 cc. of blood is indicated by the broken line. Data used for the construction of this reference line are based on Van Slyke and Sendroy's line charts with oxygen capacity expressed in terms of hemoglobin concentration using the equation: HB in grams per cent =  $O_2$  capacity in volumes per cent (corrected for  $O_2$  in solution)  $\div$  1.34. The mildly anoxic patients are indicated by open circles, those with moderate anoxia by target dots, patients with chronic cor pulmonale recovered from failure by half solid dots and those in failure by solid circles.

tension. This hypertension exists without alteration of the heart or pulmonary artery size or the electrocardiogram in all but one patient (No. 474).<sup>16</sup> It is interesting to note that the observations of cardiopulmonary function in eleven patients with chronic cor pulmonale (group C) who had completely recovered from a recent bout of right heart failure differ very little from those made in the patients with severe emphysema and anoxia who never had any evidence of cor pulmonale or cardiac failure (group B). The only significant difference, however, is that the total blood volume was somewhat greater in the group with cor pulmonale recovered from failure.

The findings in the group of patients with chronic cor pulmonale in frank congestive failure (group D) are strikingly different from those of the previous three groups. In addition to a severe degree of arterial blood anoxia (oxygen saturation = 61 to 53 per cent) there is marked polycythemia and hypervolemia and severe

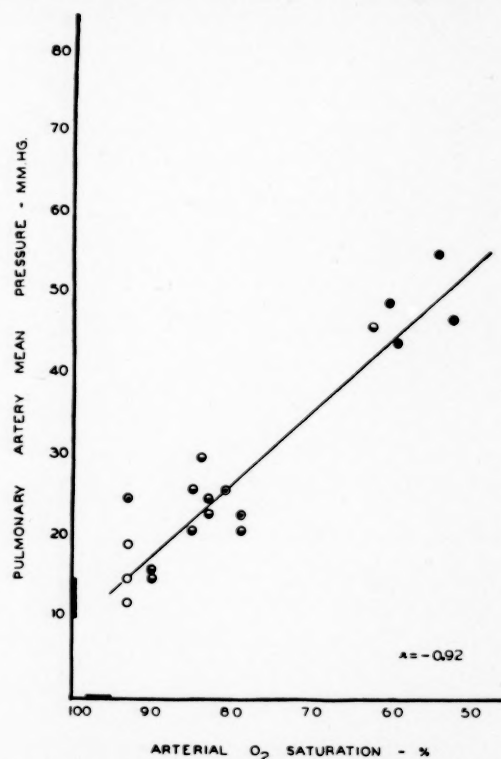


FIG. 2. Relation between arterial  $O_2$  saturation and pulmonary artery mean pressure. In this and other figures the thickened portions of the axis lines delimit the range of normal. For symbols see Figure 1.

hypochromic and therefore hematocrit readings are abnormally high while hemoglobin determinations are normal or low. This relationship between hematocrit and hemoglobin, the latter calculated from arterial blood oxygen capacity, is graphed in Figure 1. It is evident that in the groups of patients with emphysema and moderate to severe anoxia all the hematocrit values are higher than the hemoglobin would suggest.

The two patients listed in group E in Table II, despite prolonged therapy, remained in chronic congestive failure. It should be reiterated that the four patients in group D on the other hand were recompensated following treatment. The striking difference between the patients in group D and E is the much lower level of cardiac output in the latter group.

From the examination of data in the entire

group of patients with chronic pulmonary emphysema certain trends have appeared and therefore an attempt has been made to determine whether there is any significant correlation between any of the phenomena observed. The measurements of total lung volume were essen-

< 0.01), between arterial oxygen saturation and the red blood cell volume is seen. The relation between arterial oxygen saturation and total blood volume, plotted in Figure 4, while not as striking is nevertheless significant, with a correlation coefficient of  $r = -0.71$ , ( $p < 0.01$ ).

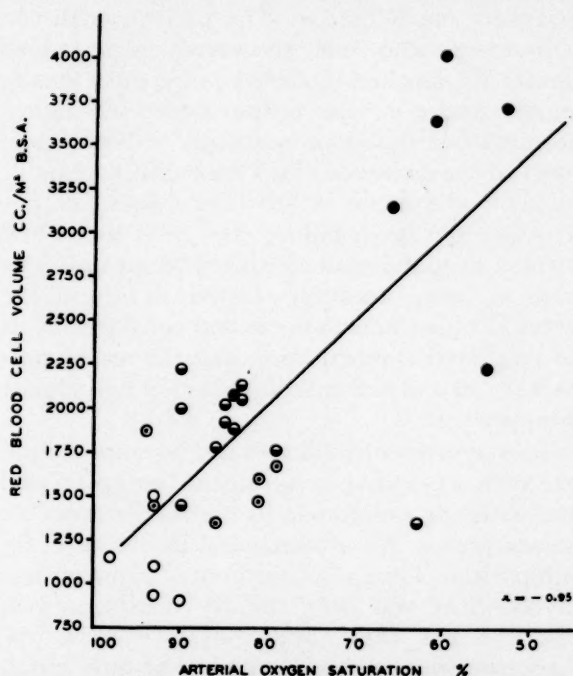


FIG. 3. Relation between arterial  $O_2$  saturation and red blood cell volume. For symbols see Figure 1.

tially the same in all five groups. Although there were significant differences in the residual air to total capacity ratio and the maximum breathing capacity between the various groups, these measurements did not vary in the same direction as did the circulatory abnormalities. For example, the patients with severe emphysema who had no evidence of cor pulmonale (group B) had a much higher residual air to total capacity ratio and a lower maximum breathing capacity than did the patients with cor pulmonale (groups C and D). However, the level of arterial blood oxygen saturation and carbon dioxide tension did appear to move in the same direction from group to group as did the circulatory changes. Indeed, as is shown in Figure 2, as the arterial blood oxygen saturation decreases, pulmonary artery pressure rises. The correlation coefficient is highly significant  $r = -0.92$ , ( $p < 0.01$ ). This is not an unexpected finding as it has been shown that acute anoxia produces pulmonary hypertension even in normal subjects. In Figure 3 the excellent correlation,  $r = -0.95$ , ( $p$

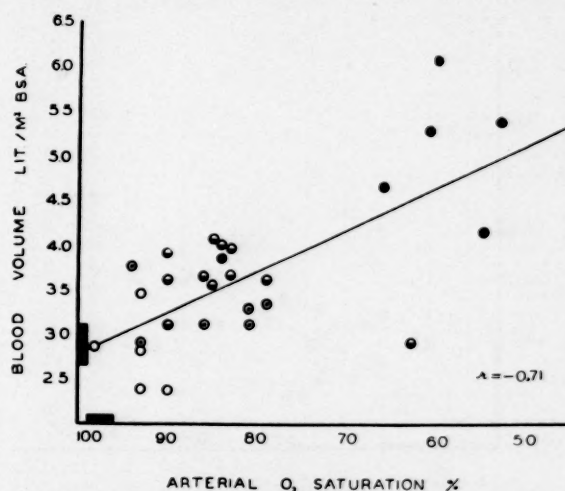


FIG. 4. Relation between blood volume and arterial  $O_2$  saturation. For symbols see Figure 1.

As is apparent, the increase in total blood volume is almost entirely a result of red blood cell increase except in those patients either in failure or recovering from failure when in some instances the plasma volume is also elevated. The plasma volume increase is probably related to the congestive state and the amount of therapy and not to anoxia which accounts for the different correlation coefficients for arterial oxygen saturation on the one hand and red blood cell volume and total blood volume on the other. Furthermore, although there is no strict relation between the level of arterial saturation and cardiac output,  $r = -0.47$ , ( $p < 0.02-0.01$ ), nonetheless a relationship exists between blood volume and cardiac output, the correlation coefficient of the latter is  $r = 0.57$  ( $p < 0.01$ ). (Fig. 5.) Thus it can be said that as anoxia increases in patients with emphysema there is apparently a rise in pulmonary pressure, total blood and red cell volume, and cardiac output.

Similar correlations were sought between the level of carbon dioxide tension ( $pCO_2$ ) and pulmonary artery mean pressure, total blood volume and cardiac index, inasmuch as there was a significant correlation,  $r = 0.80$  ( $p < 0.01$ ), between arterial oxygen saturation and carbon dioxide tension. Changes in carbon dioxide tension and pulmonary artery mean

pressure move in the same direction, with a correlation coefficient of  $r = 0.85$  ( $p < 0.01$ ). The carbon dioxide tension is also fairly well correlated with total blood volume and red blood cell volume, the correlation coefficients being  $r = 0.61$ , ( $p < 0.01$ ) and  $r = 0.78$ ,

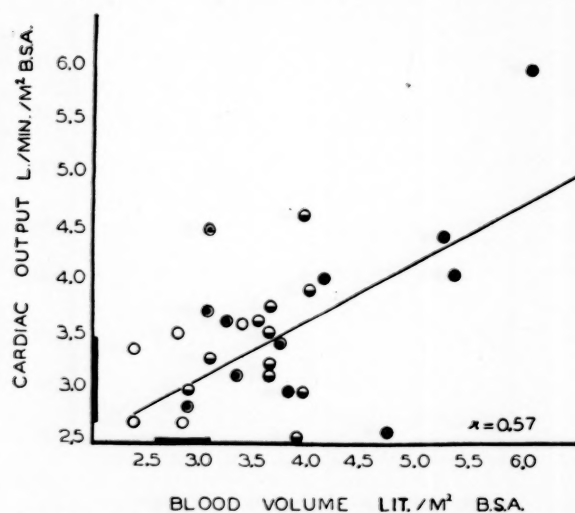


FIG. 5. Relation between cardiac output and blood volume. Mechanism of high output failure in chronic pulmonary emphysema. For symbols see Figure 1.

( $p < 0.01$ ) respectively. No relation could be found between carbon dioxide tension and cardiac index,  $r = 0.39$ , ( $p = 0.05$  to  $0.02$ ).

**Silicosis and Emphysema.** The results of cardiopulmonary function studies in a group of eight patients with silicosis and emphysema are shown in Table III (groups A, B and C). In addition to a history of industrial exposure and the typical roentgenologic evidence of fibrosis these patients all had an increased residual air and a reduced maximum breathing capacity. Again the severity of the combined lesions was judged by the degree of arterial anoxia. Those patients in group A had normal arterial blood oxygen saturation at rest but all became somewhat unsaturated after exercise. The carbon dioxide tension was increased in only one of the five patients (No. 423). Three patients with cor pulmonale studied after recovery from cardiac failure (group B) were more anoxic at rest as well as after exercise and had a higher  $p\text{CO}_2$  than those in group A, indicating a more severe degree of emphysema. The one patient with cor pulmonale studied in right heart failure (group C) also appears in group B after he recovered from failure.

It can be seen that those patients with only a mild arterial blood anoxia after exercise (group

A), who had a normal or a slightly reduced cardiac output and a normal total blood volume, nonetheless had pulmonary artery hypertension. This hypertension was not accompanied with any change in the size of the heart or the pulmonary artery, and the electrocardiographic findings were not definitive. The patients with cor pulmonale who had recovered from failure (group B) also had moderate pulmonary hypertension and a cardiac output which was either normal (two cases) or markedly reduced (one case) in the presence of a significant increase in total blood volume in all three cases. The patient in right heart failure (No. 496) had a low cardiac output in failure (listed as group C) as well as after recovery (listed in group B). Arterial blood anoxia decreased considerably as he recovered compensation and the severe pulmonary hypertension seen in failure had almost disappeared.

Two patients with silicosis and no emphysema, one without cardiac involvement (group D) and one with cor pulmonale in chronic irreversible failure (group E), are included in the series for comparison. The patient without obvious cardiac involvement was only slightly unsaturated at rest (93 per cent) and during exercise the saturation returned to normal. The only circulatory abnormality this patient demonstrated was a slight pulmonary hypertension at rest which became more marked after exercise. The patient in irreversible failure, however, was markedly anoxic and polycythemic with severe pulmonary hypertension and had an elevated right ventricular diastolic pressure. When first studied the cardiac output was within the range of normal and there was considerable increase in total blood volume and hematocrit. During the progressively downhill course over a period of six months he never recovered from cardiac failure; and although he maintained a very large blood volume, the cardiac output fell well below normal while the pulmonary artery systolic pressure reached an extremely high level a few weeks prior to death.

Since the observations are limited to such a small group of patients with silicosis, with or without emphysema, it is impossible to attempt any correlations between the level of arterial oxygen saturation, carbon dioxide tension and other measurements of pulmonary function and the hemodynamic findings. However, certain definite differences distinguish these patients from those with chronic pulmonary emphysema



TABLE III  
CARDIOPULMONARY FUNCTION IN TEN PATIENTS WITH SILICOSIS, WITH OR WITHOUT EMPHYSEMA

Case No.	Lung Volume		M.B.C. (% Pred.)	Arterial Blood			Oxygen Consump- tion (cc./min./ M <sup>2</sup> BSA)	Cardiac Output (L./min.)	Cardiac Index (L./min./ M <sup>2</sup> BSA)	Heart Rate (Beats per min.)	Peripheral Artery Pressure (mm. Hg)		Pulmonary Artery Pressure (mm. Hg)		Right Ventricle Pressure (mm. Hg) d	Blood Volume		Hematocrit (%)
				Oxygen							s/d	m	s/d	m		TBV	PV	
	Cap. (Vol. %)	Saturation %		pCO <sub>2</sub> (mm. Hg)	(cc./M <sup>2</sup> BSA)													
	T.C. (% Pred.)	RA TC × 100			R	E												
Normal	100	25	100	20.0	97	97	39	5.5	3.12	80	120/70	90	30/10	15	2900	1600	45	
(A) Silicosis and Emphysema—Mild																		
467 C. L.	107	37	59	19.2	96	89	36	4.62	2.43	75	116/66	86	33/11	20	3335	1840	45	
430 J. T.	103	39	48	16.2	96	92	43	4.66	2.81	86	117/65	86	29/13	18	3370	2065	39	
139 J. S.	104	46	55	18.9	94	91	39	4.37	2.66	65	125/63	84	32/..	..	2340	1330	43	
149 H. S.	85	50	22	19.6	95	90	40	4.40	3.06	80	128/69	90	50/..	..	2290	1285	44	
423 M. M.	81	50	50	18.2	94	88	48	5.07	3.27	83	78/55	65	29/13	21	3315	1885	43	
Average	96	45	47	18.4	95	90	41	4.61	2.84	78	112/64	82	35/12	20	2830	1685	43	
(B) Silicosis and Emphysema, Severe. Chronic Cor Pulmonale—Recently in Cardiac Failure																		
487 L. B.	82	57	47	23.8	89	75	57	5.32	3.01	84	120/75	93	50/21	36	4175	1655	60	
465 F. C.	116	56	39	22.4	87	74	48	4.96	3.10	71	.....	80	51/12	24	3785	1650	60	
496 T. A.	128	43	45	18.9	90	89	61	3.74	2.38	75	114/80	89	28/12	18	3840	2000	48	
(C) Silicosis and Emphysema, Severe. Chronic Cor Pulmonale—in Cardiac Failure																		
496 T. A.	...	..	..	17.7	76	..	61	4.25	2.39	94	129/82	94	60/31	38	....	....	..	
(D) Silicosis—Not in Failure																		
458 M.C.	63	22	63	19.6	93	97	34	5.52	3.17	68	134/79	104	30/13	19	2	2910	1655	43
(E) Silicosis—Chronic Cor Pulmonale—in Cardiac Failure (Irreversible)																		
101 A. C.	59 67 ...	39 29 ..	40 46 ..	25.6 25.5 23.3	63 62 64	.. 64 ..	52 51 58	5.79 5.18 3.94	3.55 3.20 2.43	88 80 80	163/77 158/88 146/78	101 111 103	81/.. ..... 102/..	.. .. ..	11 7 13	4500 4140 4980	1400 1320 1640	69 68 67

alone. Pulmonary hypertension was found in these few patients with silicosis regardless of the level of anoxia. Although hypervolemia and polycythemia were found in the patients with silicosis and cor pulmonale, the cardiac output tended to be low or low-normal whereas in cor pulmonale secondary to emphysema alone the cardiac output tended to be high-normal or high.

*Diffusion Fibrosis.* This group of ten patients with a variety of clinical diagnoses (Table I) demonstrated the same physiopathologic pattern which is characterized by interference of oxygen diffusion across the alveolocapillary membrane and which has been described previously as diffusion fibrosis.<sup>13,14</sup> The presence of this abnormality was demonstrated using the methods of Riley and others.<sup>17-19</sup> The usual pulmonary function studies are listed in Table IV. Characteristically the oxygen saturation was either normal or slightly reduced at rest but fell markedly after exercise while the carbon dioxide tension remained normal.

The hemodynamic pattern in the nine patients who had never been in cardiac failure was distinctive. Most of these patients had pulmonary hypertension at rest and a considerable increase in cardiac output although the total blood volume and hematocrit were normal. The tenth patient (No. 584) who had chronic cor pulmonale with cardiac failure differed somewhat from the other patients in this group; anoxia was more marked, pulmonary hypertension more severe, the right ventricular diastolic pressure was elevated and the cardiac output was considerably reduced. There were no correlations found between any of the respiratory measurements made and the hemodynamic abnormalities.

*Miscellaneous Cases.* In this last group (Table V) two of the four patients had chronic multiple embolization of the pulmonary arterial tree and in addition one (No. 526) of the two had a considerable degree of emphysema. No adequate or definite diagnosis was made in the last two patients (No. 327, No. 300) in this series. In the one patient with lung function studies (No. 300) there was no evidence of pulmonary fibrosis or emphysema. The clinical impression was that these patients had primary pulmonary vascular disease but there are no physiologic methods as yet to confirm this diagnosis.

All four of these patients were in profound right heart failure with severe pulmonary hypertension. All had moderate to severe anoxia

at rest or after exercise and the three patients in whom the blood volume was measured were hypervolemic. Two of the patients had polycythemia. The cardiac output was elevated in the patient with emphysema (No. 526) and was considerably lower than normal in the other three.

#### COMMENTS

From the data presented in this study it is apparent that although much pertinent information is available many aspects of the circulation have not been examined at all. Undoubtedly the effects of lung disease upon such functions as cardiac metabolism and energy expenditure, coronary blood flow and left ventricular performance, in addition to the measurements made, would provide a more complete analysis. Such analysis is not yet possible owing to the limitation of methods available for the study of human circulation. In these patients, however, a fairly comprehensive assay of the effects on the lesser circulation and right ventricle has been made and most of the discussion will therefore center about these data.

Less specific data are presented relative to the left heart. Nonetheless, it can be said that to date no effect of lung disease upon systemic blood pressure has been demonstrated. Certain indirect information does exist which suggests that the left ventricle is not compromised even with chronic cor pulmonale in cardiac failure. First, there was no enlargement of this chamber radiographically in any of the patients in this series and postmortem examination in eight of these confirmed this impression. Secondly, the response to acute digitalization of patients with chronic cor pulmonale in failure indicates that the left ventricle remains competent. This conclusion follows from the following observations: It has been shown that whenever pulmonary hypertension secondary to left ventricular failure existed it was abolished by rapid digitalization with digoxin.<sup>20</sup> This occurred even in patients who in addition to left-sided failure had chronic pulmonary disease as demonstrated by the patient W. H. in a previous report<sup>21</sup> whose diagnosis has since been confirmed at autopsy. If there were any element of left heart failure in patients with chronic cor pulmonale, some immediate diminution in pulmonary hypertension would be expected. This has not been observed.<sup>21</sup>

Before discussing the effects of chronic lung

TABLE IV  
CARDIOPULMONARY FUNCTION IN TEN PATIENTS WITH FIBROSIS OF THE DIFFUSION TYPE

Case No.	Lung Volume		M.B.C. (% Pred.)	Arterial Blood				Oxygen Consump- tion (cc./min./ M <sup>2</sup> BSA)	Cardiac Output (L./min.)	Cardiac Index (L./min./ M <sup>2</sup> BSA)	Heart Rate (Beats per min.)	Peripheral Artery Pressure (mm. Hg)		Pulmonary Artery Pressure (mm. Hg)		Right Ventricle Pressure (mm. Hg) d	Blood Volume		Hematocrit (%)
				T.C. (% Pred.)	RA TC × 100	Oxygen											pCO <sub>2</sub> (mm. Hg)	s/d	
	Cap. (Vol. %)	Saturation %				s/d	m												
		R										E							
	Normal	100		25	100	20.0	97					97	39	130	5.5		3.12	80	
Fibrosis—Diffusion Type																			
521 M. McD.	37	33	83	14.9	98	78	42	133	5.12	3.60	79	95/57	74	32/13	20	2160	1305	40	
501 M. B.	75	19	137	17.5	96	84	37	133	6.15	3.92	84	130/78	103	21/9	15	2470	1416	43	
534 J. H.	58	29	108	17.1	89	..	42	164	7.91	4.82	79	125/62	87	.....	..	3072	1785	42	
515 J. H.	42	26	107	14.7	96	79	41	115	5.81	3.72	96	123/83	100	35/14	23	.....	.....	..	
548 E. H.	58	28	90	18.2	94	86	43	196	7.05	4.80	107	96/63	75	35/17	26	3100	1881	43	
476 L. K.	74	25	119	20.4	94	88	31	185	8.26	4.86	100	126/75	93	30/12	19	3340	1695	49	
483 E. L.	36	32	82	17.7	96	81	37	149	5.70	3.39	82	112/69	84	24/12	17	3460	2000	42	
413 E. M.	52	46	94	17.8	88	67	39	126	5.61	3.24	91	121/69	91	58/20	34	.....	.....	..	
464 F. S.	51	27	108	17.2	90	72	43	159	5.18	3.52	115	.....	71	27/10	17	2710	1560	42	
Average	54	30	103	17.3	94	80	40	151	6.32	3.99	93	116/70	87	33/13	21	2940	1665	43	
Fibrosis—Diffusion Type, Chronic Cor Pulmonale in Failure (Irreversible)*																			
584 (a)* M. H.	36	50	67	22.3	83	63	45	128	3.30	2.25	86	147/80	105	60/28	41	3129	1370	60	
(b)†	42	44	76	19.8	77	49	43	144	3.57	2.57	92	120/59	84	70/27	44	3090	1490	52	

\* Study by courtesy of Dr. John R. West of the Presbyterian Hospital, New York City.

† A four-month interval separates studies (a) and (b).



TABLE V  
CARDIOPULMONARY FUNCTION IN FOUR PATIENTS WITH PULMONARY DISEASE OF VARYING ETIOLOGIES

Case No.	Lung Volume		M.B.C. (% Pred.)	Arterial Blood				Oxygen Consump- tion (cc./min./ M <sup>2</sup> BSA)	Cardiac Output (L./min.)	Cardiac Index (L./min./ M <sup>2</sup> BSA)	Heart Rate (Beats per min.)	Peripheral Artery Pressure (mm. Hg)		Pulmonary Artery Pressure (mm. Hg)		Right Ventricle Pressure (mm. Hg) d	Blood Volume		Hematocrit (%)
				Cap. (Vol. %)	Oxygen		pCO <sub>2</sub> (mm. Hg)					s/d	m	s/d	m		TBV	PV	
	T.C. (% Pred.)	RA TC × 100			R	E													
Normal	100	25	100	20.0	97	97	39	5.5	3.12	80	120/70	90	30/10	15	2900	1600	45		
Chronic Multiple Pulmonary Emboli—Chronic Cor Pulmonale in Failure (Irreversible)																			
344 F. E.	89	35	126	16.1	86	55	30	3.47	2.44	101	135/80	101	96/36	58	....	....	..		
Chronic Multiple Pulmonary Emboli, Emphysema, Chronic Cor Pulmonale (a) In failure (b) No longer in failure																			
526 (a) B. B.	70	56	...	15.5	76	..	58	5.76	4.42	104	147/89	112	79/39	60	3560	2030	43		
(b)	69	51	...	14.6	88	..	51	5.13	4.07	100	116/74	91	54/25	37	3060	1815	41		
Unknown Disease of Lung, ? Pulmonary Vascular Disease, Chronic Cor Pulmonale in Failure (Irreversible)																			
327 A. B.	...	..	..	21.5	58	..	40	3.29	2.30	115	128/78	96	120/55	79	3885	1650	59		
300 M. V.	113	35	55	20.5	91	78	32	3.87	2.19	59	104/64	82	72/29	44	4300	2240	48		

disease upon the lesser circuit a brief consideration of the essential characteristics of the normal pulmonary vascular bed is in order. The normal pulmonary circulation in man operates as a low pressure system. The low resistance to blood flow is a manifestation of the marked distensibility of the pulmonary arteries and their main branches and of the large capacity and deformability of the smaller vessels. It has been shown that even in the presence of a two and a half to threefold increase in cardiac output, pulmonary artery pressures remain unchanged.<sup>9-11</sup> Hence only when this limit is exceeded does pulmonary artery pressure rise with further small increments in blood flow. From these observations it appears unlikely that in normal man pulmonary hypertension exists except under conditions of severe stress. However, acute anoxia has been shown to induce pulmonary hypertension without simultaneously causing more than a small increase in blood flow. This action is probably the result of a local vasoconstriction of the pulmonary arteries or arterioles and does not involve ganglionic reflexes.<sup>22-24</sup>

Of probably the greatest importance in preventing pulmonary hypertension is the maintenance of a normal relationship between pulmonary blood flow and the capacity of the pulmonary vascular bed. In the course of chronic pulmonary disease this relationship of capacity to flow may be altered in several ways. The expansibility and distensibility of the vascular bed may be reduced by anatomic lesions, the anoxic effect on pulmonary arteries or arterioles, or both. Furthermore, polycythemia and hypervolemia resulting from anoxia engorge the pulmonary vessels and hence tend to reduce further the margin of distensibility of this bed. Increase in blood flow through such a restricted bed may produce pulmonary hypertension or aggravate an existing one. This increased blood flow may be easily induced in the course of daily activities or may result from the action of anoxia. Here again the latter acts to increase the cardiac output directly<sup>25</sup> and also indirectly by causing hypervolemia and thereby increasing the venous return. Hence in a given disease the net effect upon the circulation is governed by the relative importance of these various factors. Thus in order to clarify the circulatory changes emphasis in the following discussion will be placed first upon the basic changes induced by each disease process and then upon the cortège of complications which spring from them.

From an examination of the data presented it appears evident that circulatory changes in chronic pulmonary emphysema can be related to both an anatomic alteration of the pulmonary vascular bed and to anoxia. The disease process, by thinning or rupture of the alveolar septa and development of bullae, may reduce the number, caliber and expansibility of the smaller vascular channels. In the absence of significant anoxia this restriction of the vascular bed may not be extensive enough to produce pulmonary hypertension at rest (group A) but any temporary increase in blood flow, as during daily activities or in the course of an infection for example, will favor pulmonary artery pressure rise. If the disease is more advanced, and restriction of the vascular bed more extensive or anoxia is present or both, pulmonary hypertension at rest may occur (group B). In these patients two of the sequelae of chronic anoxia, namely, an increased cardiac output and polycythemia are not marked. Anoxia, therefore, appears to act chiefly in these patients upon the tone of the pulmonary arteries or of the arterioles. The degree of hypertension that results is apparently often not severe enough to cause clinically detectable hypertrophy of the right ventricle although it is not unlikely that minor degrees of hypertrophy may exist. The situation is analogous to that observed in systemic hypertension with concentric hypertrophy of the left ventricle.

The more marked degrees of pulmonary hypertension seen in patients with chronic cor pulmonale in failure (group D) might be construed as the result of more extensive reduction in expansibility and capacity of the vascular bed due to the emphysematous process itself. However, in view of the reversible nature of this hypertension, as demonstrated by the fact that all the patients in this group had a marked reduction in pulmonary artery pressures after treatment and appear at rest only mildly hypertensive or normotensive when recovered (group C), it would appear that anoxia, which also diminished in response to therapy, was more likely the predominant agent.

The importance of anoxia in emphysema is evident from a consideration of the following: Chronic anoxia, with its sequelae of arterial or arteriolar constriction, polycythemia, hypervolemia and increased cardiac output, perpetuates a vicious cycle of physiologic abnormalities. Each of these sequelae in turn affects the others.

Hypervolemia, by increasing the volume of blood in the venous system, effects an increased stroke volume and output. It also limits further the distensibility of an already restricted pulmonary vascular bed. The increased blood flow operating in the face of a reduced vascular capacity tends to maintain a high pulmonary artery pressure. Red blood cell increase by its effects on blood viscosity may possibly be an enhancing factor in the production of pulmonary hypertension. It is at this stage that right ventricular hypertrophy or some degree of dilatation becomes manifest. The stage is then set for the appearance of right heart failure although many patients with chronic pulmonary emphysema never go beyond this phase, maintaining compensation despite a moderate hypervolemia, pulmonary hypertension and elevated cardiac output.

We do not know, in all instances, what is the precipitating factor in the break in right ventricular compensation but often a bout of acute anoxia is the trigger mechanism. This may accompany attacks of bronchiolar obstruction or a severe pulmonary infection. The acute anoxia superimposed on chronic anoxia further stimulates the rapid formation of hypochromic red blood cells.

Presumably under the combined assaults of these separate factors (high cardiac output, marked pulmonary hypertension, direct action of anoxia on the strained right ventricular myocardium and an increased blood volume) the optimal stretch of the myocardial fibers is exceeded and right ventricular failure follows. This state of cardiac failure is characterized by an impairment in the emptying of the right ventricle and, therefore, the stroke volume is reduced from a previously higher level; by an increase in residual diastolic blood volume and by an elevation of the end diastolic filling pressure of the right ventricle. The paradox of a high cardiac output in the presence of failure is thus explained by the state of the circulation just preceding the failure of the right heart.

Intrinsic myocardial damage being as a rule limited and not comparable to what is found in coronary disease and rheumatic myocarditis, the failure is easily reversible if proper therapy is instituted. This is evident also from the fact that the state of the cardiopulmonary function in those patients who had recovered from failure (group C) did not differ markedly from those without known cardiac involvement (group B).

Although pulmonary hypertension is only moderate at rest, it is likely that most of these patients do have a considerable increase in pulmonary artery pressure whenever there is an increase in cardiac output. This fact is illustrated by one patient (No. 582) in group C whose pulmonary artery pressure rose from a normal figure at rest,  $27/8$  with a mean of 16 mm. Hg to  $38/14$  with a mean of 24 mm. Hg while the cardiac output increased 55 per cent following a mild leg exercise of ten minutes' duration. This could not be interpreted as an effect of anoxia as the leg exercise was not accompanied with a fall in arterial oxygen saturation. It was rather an indication of some degree of anatomic restriction of the vascular bed.

It can then be assumed that if the duration and severity of pulmonary hypertension regulate the degree of right ventricular hypertrophy, the latter in these patients depends upon the persistence and severity of anoxia plus the anatomic restriction of the pulmonary vascular bed and the degree of physical activity dictated by their life situation. Cardiac failure is reversible and even can be prevented as long as these factors are controlled. If, however, these cases are left untreated, are treated improperly or have reached the end stage of their disease when relief of anoxia is no longer possible, deterioration of the myocardial fibers leads to reduction in cardiac output which in the irreversible cases (group E) becomes lower than normal.

This concept of the development of chronic cor pulmonale in emphysema, while suggested by the over-all data herein presented, grew principally out of serial measurements made in individual patients at various phases in their disease. Although it has not been possible to study any one patient just before and then immediately after the onset of right heart failure, it has been possible to observe them in failure during and after recovery of compensation.<sup>21</sup> Furthermore, recently several patients have been followed for one and one-half to two years after their initial bout of failure and repeated physiologic measurements—in particular determinations of blood oxygen saturation, carbon dioxide content and blood volumes—have served as checks upon their condition. Alerted by changes in these measurements, it has been possible for us to prevent cardiac failure in these patients for a long period of time.<sup>26</sup> Invariably the danger signals in their clinical course were increasing anoxia and hypervolemia. The



findings in the patient No. 489 (groups B and C) emphasize the fact that hypervolemia exists for some time before the onset of failure in these cases.

Hence it must be stated that the broad concept of the pathogenesis of chronic cor pulmonale is based upon observed data and, while several of the successive steps have not been observed in their exact chronologic order, nevertheless the schema as outlined best conforms with the actual facts as well as integrates them satisfactorily.

In summary, then, it can be said that in chronic pulmonary emphysema anoxia is the dominant and all important abnormality as far as the circulatory complications are concerned. As emphasized in previous papers on emphysema<sup>12,27</sup> the element of bronchiolar spasm and obstruction is primarily responsible for the anoxia. There must be some anatomic alteration of the vascular bed in these patients but this remains less prominent in most instances.

Analysis of the relative importance of anoxia and reduction in the capacity of the vascular bed is more difficult in the group of patients in whom silicosis and emphysema coexist. Nonetheless, it is interesting that in the presence of only a minimal degree of anoxia a normal blood volume and cardiac output, significant pulmonary hypertension exists in some of these patients (groups A and D). This certainly suggests that the fibrotic process has of itself effected a considerable reduction in the vascular capacity. The sequelae of anoxia are apparent, however, in the other groups (B and C) although it is noteworthy that the cardiac output was not elevated. It is difficult in these more advanced cases to ascertain the respective roles of arterial blood anoxia and the reduced vascular bed in producing pulmonary hypertension. The importance of the anoxic factor is emphasized in one patient (No. 496) whose severe pulmonary hypertension almost disappeared after recovery from cardiac failure concomitantly with a decrease in arterial unsaturation.

Because few patients with silicosis were studied, an outline of the pathogenesis of chronic cor pulmonale in this disease cannot be stated with certainty. The finding of pulmonary hypertension even in early cases points to the predominance of the basic anatomic factor and suggests that the hypertension is irreversible unless some part of it is due to anoxia. Furthermore, the normal or low cardiac output indi-

cates that the course of these patients is unlike patients with cor pulmonale due to emphysema. Persistent pulmonary hypertension undoubtedly predisposes to right ventricular hypertrophy. If hypertension is severe it leads ultimately to irreversible cardiac failure whereas the intermittent type of pulmonary hypertension seen in emphysema, in which the variable anoxia controls the pressure rise, is less likely to result in chronic cardiac failure.

Analysis of the results in the group of patients with diffusion fibrosis is somewhat more complicated because of the diversity of disease processes represented (see Table 1) and lack of knowledge as to the type and extent of the pathologic lesions. It is merely because of the similarity of their cardiopulmonary dysfunction that they are grouped together. It seems unlikely that anoxia plays an important role in producing the circulatory changes since arterial unsaturation is minimal at rest and since polycythemia, one of the early sequelae of chronic anoxia, does not occur in the majority of these patients. Probably, then, the pulmonary hypertension results from an anatomic reduction in the capacity of the pulmonary vascular bed. This is brought out by the reaction to stress in one of these patients. Following ten minutes of a mild leg exercise and presumably after reaching a steady state this patient (No. 476) who was mildly hypertensive at rest had a further increase in pulmonary artery pressure with only slight arterial unsaturation.

There is as yet no adequate explanation for the high cardiac output in this group. Suffice it to say that it is not apparently on a hypervolemic basis, in contrast to the patients with emphysema, when the increased blood volume is an important factor in the production of the increased systemic blood flow. It should be recalled that these patients have histologically active and progressive pulmonary lesions which may in some instances be part of a systemic disease, in contrast to the more or less static nature of emphysema and silicosis, and that the activity of their disease may account for the high output.

Patients with this type of progressive pulmonary disease frequently die of pulmonary insufficiency before chronic cor pulmonale has developed. When the latter is seen, (No. 584) the hemodynamic picture is not unlike that of silicotics with right heart failure and this points to the primary importance of the anatomic alterations of the vascular bed and the irreversi-

bility of the pulmonary hypertension. The finding of a low cardiac output may mark the terminal phase in these patients. This patient (No. 584) died six months after her first cardiac catheterization. It is also interesting that a change from a slightly elevated cardiac output (3.72 L./min./M<sup>2</sup>BSA) to a much lower output (2.69 L./min./M<sup>2</sup>BSA) has been noted in one patient (No. 515) at the time right heart failure developed.

The extreme pulmonary hypertension in the group of patients with pulmonary diseases of varying etiologies indicates extensive reduction of the pulmonary vascular bed. This was confirmed by autopsy in two of the cases. Obviously the effect of anoxia may be superimposed upon the anatomic lesion as indicated by the two studies in one patient (No. 526). Cardiac failure was irreversible in three of the patients, each of whom had a low cardiac output, once again pointing to the probability of a damaged myocardium.

In reviewing the circulatory complications of chronic pulmonary disease in these forty-eight patients one is struck by the variability of the findings. It is true that pulmonary hypertension appears consistently throughout most of the groups examined but the level of blood flow (cardiac output) and blood volume vary in the different disease processes. However, certain patterns of circulatory change specific to the diseases do emerge. Clinically, it is pertinent to ask how one can detect the advent of circulatory alterations and what should be done to forestall them. From the data on emphysema it would seem that most of the circulatory complications—pulmonary hypertension, high output and increased blood volume—stem from anoxia. Although one cannot set forth an invariable rule, it does appear evident that once the arterial saturation falls below 90 per cent at rest a train of circulatory abnormalities occurs. We do not know to what extent the pulmonary pressures, already increased at rest, will rise on exertion in such cases. This aspect of the problem is being investigated at present. Certain it is that the duration and degree of the pulmonary hypertensive episodes, as well as their frequency, must be closely related to the development of right heart hypertrophy.

The reversible nature of the circulatory alterations in chronic cor pulmonale in emphysema should afford great impetus to therapy in a group of patients which heretofore has been

regarded as therapeutically almost hopeless. This pessimistic impression is perpetuated even in modern textbooks and remains viable primarily because the basic physiologic disturbances in this disease have been imperfectly understood and little differentiation made between manifestations of pulmonary insufficiency and cardiac failure. It has even been stated that digitalization gives poor results in patients with cor pulmonale in failure. Since it has been demonstrated that the failing ventricle does improve with digitalization,<sup>21</sup> it is more likely that the poor results reflect neglect of the pulmonary insufficiency and its sequelae. Since the latter is parent to the cardiac complications, therapy should be directed at correction of both cardiac and pulmonary dysfunction. Briefly, optimal treatment consists essentially in the relief of pulmonary infection by antibiotics, of bronchiolar obstruction and reduction of bronchial secretions by the liberal use of atomized bronchodilators, improvement of the function of the right ventricle myocardial fibers by digitalization and, finally, reduction of the hypervolemia by phlebotomies. Oxygen therapy is beneficial also but it should not be used continuously for fear of the development of carbon dioxide narcosis.<sup>28,29</sup>

The circulatory complications of silicosis have only been touched upon. It appears from pathologic studies<sup>30</sup> that the pneumoconiotic nodular process in some cases is located predominantly about vascular channels. It seems likely that the few patients studied here fell under this category. Progression of the lesions leads inexorably to persistent pulmonary hypertension and ultimately to irreversible right heart failure. Even rigorous restriction of physical activity, directed at minimizing exacerbations of pulmonary hypertension, will not protect the patient from progressive and eventually terminal heart failure. It is reasonable to suggest that until better studies are available in all forms of fibrosis physical exertion should be curtailed, as it is only by maintaining as low a pulmonary blood flow as possible that right heart strain can be minimized. If emphysema coexists with fibrosis, vigorous therapy towards its sequelae is, of course, of equal importance. In any event, the eventual prognosis as far as the circulation is concerned can be better appreciated if these fundamental concepts are known.

A word more remains to be said about chronic cor pulmonale. Up to the present the criteria



for the diagnosis of this secondary form of heart disease have perforce been overly simplified.<sup>31</sup> Since we know that pulmonary hypertension may exist early in the course of chronic lung disease, it is apparent that the natural history of cor pulmonale must be restated. This obviously begins with the stage of pulmonary hypertension. This phase may be prolonged and difficult to recognize except by inference. Nonetheless, it is during this period that therapeutic interference will be most useful. Whether minor degrees of right ventricular hypertrophy or dilatation always exist in the presence of pulmonary hypertension is impossible to determine. However, with the appearance of dilatation of the pulmonary artery or right heart hypertrophy it would seem logical to utilize the term cor pulmonale, compensated. Right heart enlargement often defies detection, however, either by roentgenogram or electrocardiogram,<sup>16</sup> making the diagnosis of cor pulmonale in certain cases exceedingly difficult. It remains for the clinical physiologist to indicate means of identifying the various stages of cor pulmonale by pragmatic methods. This has been attempted in this paper for the group of patients with emphysema and it has been shown that measurements of arterial blood oxygen saturation and carbon dioxide content, as well as blood volume and hematocrit, can serve as indicators of the expected circulatory changes.

The problem is much more difficult in the other forms of chronic pulmonary disease discussed in this report and much more work is required before similar material becomes available.

No attempt has been made in this report to discuss the effects of chronic lung disease and its sequelae in patients with heart disease other than chronic cor pulmonale. This most interesting subject is being investigated. Furthermore, the dynamics of acute cor pulmonale, whether due to overwhelming pulmonary infection with anoxia or thromboembolic phenomena, have not been considered.

#### SUMMARY

1. Studies of both cardiac and pulmonary function were made in forty-eight cases of chronic pulmonary disease. The pathogenesis of pulmonary hypertension and the evolution of chronic cor pulmonale have been considered.

2. Pulmonary arterial hypertension was present at rest in thirty-nine of the forty-eight patients studied.

3. In chronic pulmonary emphysema anoxia was shown to be the important abnormality since it was directly or indirectly responsible for the circulatory complications found in these patients. The reversible nature of these circulatory complications in emphysema was demonstrated and its importance with regard to therapy was stressed. It would appear that in patients with chronic cor pulmonale and emphysema cardiac failure is generally characterized by a high cardiac output.

4. In patients with silicosis and emphysema the pulmonary hypertension is less likely to be reversible since it stems from anatomic alterations in the pulmonary vascular bed rather than from anoxia. When chronic cor pulmonale and cardiac failure develop in this type of patient, the cardiac output is not elevated. This emphasizes the point that chronic cor pulmonale in failure is not always of the high output type.

5. The circulatory changes found in the group of patients with diffusion fibrosis do not appear to be related to anoxia but probably spring from the anatomic lesions produced by the disease processes themselves.

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# Combined Staff Clinic

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## Meningitis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. YALE KNEELAND: Before proceeding to the subject of today's clinic, the management of meningitis, I should like to make some general comments on diagnosis in the patient with meningitic signs. There are two cardinal errors which are all too common in this connection. One is to fail to think of meningitis as a diagnostic possibility until valuable time has been lost, the other is to start treatment in a vast flurry of excitement without any precise reasoning as to etiology.

Now, it is impossible to mistake the florid picture of meningitis. The patient presents himself with high fever, bursting headache, delirium and violent spasm of the extensor muscles of the neck and back. This almost invariably stimulates medical thinking along appropriate lines. On the other hand, it is in the case of those patients with more subtle manifestations of meningitis that we are likely to overlook it as a diagnostic possibility unless we have a high index of suspicion.

The possibility of meningitis must be entertained in all acutely ill patients, particularly in young adults. Admittedly, when anyone is taken acutely ill it is often assumed that the patient has a common respiratory infection. Now, there are certain clinical features that are not part of the common respiratory diseases, generally speaking; for example, severe and persistent headache. I admit there are certain exceptions to this but the existence of severe and persistent headache in an acutely ill individual ought at least to suggest the possibility of meningitis, as well as certain other possibilities such as infectious mononucleosis or rickettsial disease. Repeated vomiting, in adults at any rate, is not a feature of common respiratory infection. Neither are lethargy or stuporousness. All of these symptoms should suggest the possibility of involvement of the central nervous system. Moreover, with the exception of bacterial pneumonia and

streptococcal pharyngitis, most of the common respiratory epizootics are not associated with leukocytosis, and the existence of leukocytosis in an acutely ill young individual who does not have exudative pharyngitis or clinical manifestations of pneumonia should put one on guard. The cardinal sign of meningeal irritation, of course, is stiffness of the neck. This should be carefully searched for in every acutely ill individual, indeed repeatedly searched for, as it is a sign which may appear abruptly.

The treatment of bacterial meningitis is different from the treatment of the non-bacterial varieties of meningitis. Moreover, the treatment of the various types of bacterial meningitis is not the same; hence again the paramount importance of precise etiologic diagnosis whenever this is humanly possible. I do not want to imply that if one is visiting a lumber camp and finds someone with an abundant purpuric rash and stiff neck one should withhold penicillin until the spinal fluid is flown to a good laboratory many thousand miles away. I simply want to emphasize that if chemotherapy and antibiotics are started before the necessary items are obtained for precise bacteriologic diagnosis, negative findings lose their significance and the physician is then faced with an all too common and distressing situation in which he is forced to treat a continuing infection the nature of which is totally obscure. It also follows from this that the habitual use of small doses of chemotherapy and antibiotics in common, nondescript, everyday respiratory infection will very successfully obscure the diagnosis of meningitis if this disease is in fact developing. I grant you it is a little utopian for me to suggest to those of you who are going to practice medicine in the home—and I suppose a few will—not to treat people with penicillin before you have done a complete hospital workup. But I do wish to point out this is true, that small doses of anti-



biotics will obscure the precise diagnosis. So, pray, if you are working in places other than lumber camps try to defer initial treatment at least until a specimen of spinal fluid has been obtained.

Spinal fluids divide themselves into two broad classifications: those that are grossly turbid and those which are clear or only very slightly hazy. Fluids of the former category, that is to say grossly turbid, are an indication for immediate treatment as they point invariably to bacterial meningitis. These turbid spinal fluids, of course, are characterized by a preponderance of polymorphonuclear leukocytes and marked reduction in spinal fluid sugar content. Not all bacterial agents produce grossly turbid fluid. The tubercle bacillus for example does not, and neither does the *Cryptococcus hominis*. In neither instance, however, is immediate treatment indicated; treatment should, in fact, be withheld in affairs of this kind until the precise diagnosis is made. Non-bacterial agents produce fluids that are grossly clear or only slightly hazy. These fluids, generally speaking, resemble the fluid of tuberculous meningitis in that the predominant cell type is the lymphocyte. However, there is one striking and important difference and that is the level of the spinal fluid sugar. It can be generally stated that non-bacterial agents which cause a meningitis or meningo-encephalitis do not reduce the spinal fluid sugar.

It follows from what we have said that immediate treatment is indicated in all instances in which the fluid is grossly turbid and should be withheld in almost all cases in which the fluid is grossly clear or only very slightly hazy. The exception here is in the fluid which is only slightly hazy but contains a preponderance of polymorphonuclear leukocytes. We occasionally see a very early case of bacterial meningitis in which the total count is low initially. It is true that in certain viral diseases, for example in poliomyelitis, the early cytology of the fluid may be preponderantly polymorphonuclear. This has also been noted in certain outbreaks of aseptic meningitis but in such instances, particularly if the patient seems acutely ill and there is a leukocytosis in the peripheral blood, it is probably safer to assume the presence of early bacterial meningitis.

To return to the patient with grossly turbid spinal fluid. If a rash is present, the diagnosis of cerebrospinal fever or meningococcic meningitis is an overwhelming statistical likelihood. That,

however, except in unusual circumstances, should not violate our general principle of obtaining spinal fluid for examination before the initiation of treatment.

In bacterial meningitis there is an inflammation of the pia arachnoid, with conversion of cerebrospinal fluid into a purulent exudate. In addition to this purely local affair there are three main immediate secondary effects. One is the penetration of the infection in the direction of the parenchyma of the central nervous system by means of the Virchow-Robin spaces. Another is the accumulation of sufficient amounts of fibrin in the exudate to block the circulation of the cerebrospinal fluid at one or another of the key foramina and aqueducts through which it flows, with resulting internal hydrocephalus. Third is the involvement of emergent nerves, particularly of those cranial nerves which travel a long way over the base of the brain. These facts must be borne in mind in any attempt to treat bacterial meningitis.

Meningococcic meningitis is not a very ancient disease in medical history. It was first reasonably well described in 1805 in Geneva and again the following year in Medfield, Massachusetts. It was in 1877 that Weichselbaum wrote his classic paper in which he described the postmortem findings in six cases and identified the *Neisseria meningitidis* as the cause of the disease. It was soon learned thereafter that the meningococcus was the cause of almost all epidemic meningitis and of the great majority of sporadic cases of meningitis at that time. To give you some notion of the importance of meningitis as an acute infectious disease, I should like to cite the Glasgow epidemic in 1907. There were 998 patients, of whom 715 died, a case fatality rate of 70 per cent. Shortly thereafter serum therapy was introduced and very widely and skillfully employed. Between the years 1920 and 1936, when serum was universally used in the treatment of this disease in the United States, the figures from twenty-two American cities indicated that the case fatality rate was 51.2 per cent, a reduction of only about 20 per cent from the older figures in untreated epidemics. This could hardly be called a thoroughly satisfactory state of affairs, and it was a very depressing experience for all of us to realize that in spite of the extraordinary efforts we made with serum the effects were so dismally unimpressive.

The meningococcus, as you know, is a gram-negative diplococcus which is flattened per-



pendicularly to its long axis. It is a delicate bacterium, very thermolabile and rather difficult to cultivate. In exudates it tends characteristically to occupy an intracellular position, appearing in the cytoplasm of polymorphonuclear leukocytes unless the infection is overwhelming, when masses of the organisms may be seen growing freely outside of the polymorphonuclear leukocytes. This, however, is relatively rare and it is by no means uncommon to have so few organisms demonstrable in the spinal fluid that direct smears and Gram stains examined late at night by the house staff may be a source of real confusion. The meningococcus is a strictly human parasite with a peculiar predilection for the coverings of the brain and spinal cord. It exists in the normal population in a carrier state and many surveys have been made to determine the incidence of carriers. The carrier rate in any given community bears some relation to the incidence of the clinical disease but the organism has been found in every urban community in which sufficiently consistent efforts have been made to isolate meningococci from the normal nasopharynx. All of the three types, I, II and IIa, have been recovered from normal carriers who did not have meningitis and who did not develop meningitis. Some carriers are evidently semi-permanent; others are transitory carriers, and the assumption is that in the sporadic case the carrier either becomes infected with his own organism or hands it to a friend who at the moment is in a state of maximal susceptibility to infection. The factors governing susceptibility are, of course, unknown.

Of great interest is the extraordinary sensitivity of *Neisseria meningitidis* to the sulfonamides. It was shown in Australia in 1940, and subsequently confirmed on a very large scale in the U. S. Army Fourth Service Command in 1942, that very small doses of sulfonamides given over a very short period of time would effectively eradicate the carrier state of meningococci in the overwhelming majority of individuals. From this observation there grew the modern epidemic prophylaxis of the disease. When meningitis appears nowadays, particularly in communities like Army camps where the number of susceptibles presumably is great, small amounts of sulfadiazine are given for a day or two to those at risk. The result of this is not only that the carrier state is almost quantitatively eliminated, but the epidemic, if it is under way, will arrest itself immediately and permanently. It is per-

haps on this account, and the general widespread use of sulfonamides, that there has been a marked diminution in the number of cases of meningococcal meningitis. We have had only five cases in the last five years in the Presbyterian Hospital.

I am sure you are familiar with the classical description of the disease. The *catarrhal stage* is indistinguishable from minor respiratory infection. The *septicemic stage* usually is abruptly initiated with chill and high fever, with or without rash which is characteristically purpuric in type. After a variable length of time, or after no length of time at all, there appears the third, the metastatic or *meningeal stage* in which the symptoms are those of meningitis. Now, I want to call your attention to the variations which occur in this classical picture of meningitis as described in the textbooks. The catarrhal stage may be totally unrecognized. There may be no recognized septicemic stage. On the other hand, the septicemic stage may persist either in acute or subacute to chronic type without the development of the metastatic or meningeal stage. Furthermore, I think it is worthy of note that the febrile curve in meningitis is variable. Most patients show an elevation of temperature; often it is high. On the other hand, some patients are afebrile. I had occasion during the war to see two soldiers who had afebrile cerebrospinal fever evacuated from the forward areas with the diagnosis of combat exhaustion; and this, gentlemen, is a serious error in diagnosis, for while an amyntal interview under these circumstances might be fraught with interest, its therapeutic effectiveness is undemonstrable.

Now to get to our main subject, the treatment of bacterial meningitis, again let me emphasize that the key is early diagnosis. The second thing I should like to point out is that, in our opinion at least, sulfadiazine is still the cornerstone of the arch of therapy of cerebrospinal fever. I say this for three reasons: (1) because of the extraordinary sensitivity of the meningococcus to sulfonamide; (2) because of the ready penetration of sulfadiazine into the cerebrospinal fluid; (3) because of the extraordinarily good results that were obtained with this agent alone before the introduction of penicillin. In the year 1944 the case fatality rate for meningococcal meningitis in one Army overseas theatre was just a decimal point above 2 per cent.

Let us now consider the treatment of cerebrospinal fever and divide our cases for schematic

purposes into three types: First, *the average case*. With the average case one first does a lumbar puncture for diagnosis, also blood, nose and throat cultures if possible, and a leukocyte count. If the lumbar puncture has disclosed a turbid fluid, the patient is treated with parenteral sulfadiazine, the traditional dose being 5 gm. dissolved in 1 L. of saline. That can be given by fairly rapid intravenous drip and as most of these patients are dehydrated it is often customary to follow this with 500 cc. of a sixth molar lactate solution, with a view to alkalinizing the urine and, admittedly on somewhat tenuous grounds, of thereby reducing the likelihood of the development of sulfonamide nephrosis. It follows without saying that in any patient on sustained sulfonamide treatment there must be a careful watch to ward off the familiar side effects of the sulfonamides, which I shall not go into here. A blood level of 12 to 15 mg. per cent should be maintained and some four or six hours after the initial infusion one should get a blood level of sulfadiazine to make certain of this. How one proceeds further with sulfadiazine therapy depends on, (1) the level which has been obtained following the infusion and (2) whether the patient is able to take sulfadiazine by mouth. One often can pick up at this point with oral administration of a gram every four hours; occasionally if the level seems low on that regimen, it may be wise to increase the dosage to  $1\frac{1}{2}$  gm. every four hours.

The question of penicillin therapy now introduces itself. Well, I should say: why not? Why not give intramuscular penicillin at the time of initiation of the sulfadiazine treatment and perhaps keep this up for a day or two? It can do no possible harm. Penicillin has a shorter latent period in its antibacterial action than sulfadiazine and, although I do not think one can demonstrate it statistically, it perhaps might increase the survival rate a little.

Now as to duration of treatment in meningococcal meningitis, I think a minimum of a week is indicated although we have noted in individuals dying from other causes that within four or five days of the initiation of therapy, even in severe meningitis, the meninges appear grossly normal at autopsy.

What should be the expected result of this therapy? Twelve hours after institution of therapy the patient should be clinically improved. The temperature should have started falling and the sensorium should be clearing.

By twenty-four hours there should be very marked improvement and the temperature is likely to be normal, although the neck at this time is usually still rigid. After forty-eight hours the rigidity of the neck in the mild case is, as a rule, less evident, the headache has almost totally disappeared and the patient appears well on the road to recovery. The question always arises as to the desirability of repeated lumbar punctures. I think that the indications for repeated lumbar puncture in the treatment of the average case are two in number: One is for the relief of symptoms such as persistent, severe headache, respiratory difficulty, poor vital signs in general, persistent delirium, etc.; the other is for general appraisal of the efficiency of treatment in any case in which a totally satisfactory result is not obtained. In other instances I think it is quite safe to let the patient coast along through his uncomplicated convalescence without repeated lumbar punctures. A very carefully controlled study has indicated that patients who are not repeatedly tapped do a little better than those who are.

The next category is *the severe case*, and by severe I mean those in whom the onset is unusually fulminating or in whom treatment has been long delayed. Here one uses precisely the same technic of sulfonamide administration but adds to it intrathecal penicillin in doses not exceeding 20,000 units given in at least 5 cc. of saline solution at the time of initial lumbar puncture, together with large doses of aqueous penicillin intramuscularly at three hourly intervals.

Lastly, there is the so-called *Waterhouse-Friderichsen syndrome*, which is meningitis accompanied by severe shock due to peripheral vascular failure. Here the treatment is the same as in the severe cases except that one treats the shock as well. Now, in the Waterhouse-Friderichsen syndrome an acute insult to the adrenals has often been described at autopsy, and the question always arises as to whether replacement therapy is indicated when this clinical syndrome manifests itself. I shall defer this question—perhaps at the end of the hour Dr. Loeb would be willing to give his views on the subject. In any event it seems to me that the cardinal principle in the therapy of the Waterhouse-Friderichsen syndrome is the treatment of shock, and blood transfusions are almost invariably the essential feature. Electrolyte solutions alone are disappointing in restoring the



peripheral circulation. In addition one should maintain large doses of penicillin for several days and I think it is probably wise to keep up lumbar punctures at twelve-hour intervals, introducing penicillin in the above cited dosage for a day or two, with daily lumbar punctures for several days thereafter.

That is all very schematic and easy, and it makes the problem sound a little too simple. Therefore let us now look at an actual case and see what happens when one treats a patient and not a mythologic character in a textbook. Mrs. K., a sixty-one year old lady, was admitted to this hospital six days ago. You can, I think, appreciate that she now looks pretty well. You can see the extensive herpetic eruption about the lips, which is a very characteristic feature of cerebrospinal fever, and some of you can see fading purpura of the extremities. As I said, the patient is sixty-one years old. She is too old to get cerebrospinal fever in the first place. Her past medical history is inconsequential. She works in a store as a saleslady. A week ago today she was at work, and at exactly this hour she suddenly felt chilly sensations and general malaise and went to the store physician who took her temperature and found it to be 102.6°F. He told her she had the gripe and sent her home. When her husband arrived home at seven o'clock in the evening, he found she was quite ill. She had by now a fairly severe headache; her fever was about the same. The patient awoke in the morning with a normal temperature, mark you that, but during the morning she became progressively drowsy and by noon her temperature was 102.5°F. At this point her doctor sent her to the Presbyterian Hospital. On entry here she was found to be in a low muttering delirium approaching coma, and had a profuse purpuric rash. Everyone here was somewhat concerned about the age of the patient, and it was believed that in this acutely ill individual, although the systolic blood pressure was well maintained and there had been no clinical history suggestive of cardiovascular disease, one should proceed cautiously with the intravenous administration of fluids. Consequently her sulfadiazine was presented to her in the form of two-gram doses at three or four-hour intervals, initially subcutaneously in 200 cc. volume with a certain amount of hyaluronidase to increase the rate of absorption. She was also treated with intrathecal penicillin in 10,000-unit doses in 5 cc., and she was given a million units of peni-

cillin every three hours intramuscularly. That is probably ten times more than is necessary but in any event penicillin is cheap, human life was at stake, and we did not spare the expense. By midnight things seemed to be reasonably favorable. She was still comatose but she had had some urinary output on admission and the systolic blood pressure was maintained. However, in the early hours of the morning after admission she suddenly had a rather catastrophic fall in blood pressure and developed what was by definition the Waterhouse-Friderichsen syndrome. The patient was comatose although afebrile. The systolic blood pressure was 90, diastolic about 70, the pulse thready and poor indeed. The situation looked rather bleak and at that point measures were instituted to treat her shock. An indwelling catheter was introduced and those watching at the bedside noted that the dripping became progressively slow until virtual anuria was established. The question arose at that time as to whether we were dealing with a sulfonamide nephrosis. Now, that seemed highly improbable to me. In the first place, very few people develop sulfonamide nephrosis as rapidly as this. In the second place, by that time it was known that the blood urea nitrogen was somewhat elevated and that the blood sulfonamide level was very high, 20. It seemed more likely, therefore, that this patient was suffering from the effects of her dehydration and peripheral vascular failure and hypotension, and that her oliguria was due to those causes rather than to sulfonamide nephrosis. In view of the possibility, however, sulfonamides were discontinued and have not been given since. During the day treatment for shock and dehydration was instituted and she was also given one injection of 5 cc. of adrenal lipo-extract, a matter which possibly Dr. Loeb will comment on later, and the lumbar puncture was repeated. Interestingly enough, while the first cell count before treatment was only 1100, the second was in the neighborhood of 20,000, and organisms could still be seen in the smear. Culture, however, showed that they would not grow. During that afternoon and evening the blood pressure rose slowly and the urinary output began to increase. By the next day the situation had rather dramatically and very gratifyingly changed in regard to the meningitis. The patient was out of coma. She was rational and her blood pressure was relatively normal, or at least it was at a better level. Her urinary output was im-



proving steadily. However, a new manifestation had developed, and that was abdominal signs suggestive of generalized peritonitis. There was distention together with marked generalized tenderness, notably in the right lower quadrant. Spasm was marked on the right side and there was extreme rebound tenderness everywhere. Various diagnostic possibilities suggested themselves. It was thought possible that this was due to purpura occurring in the abdominal cavity. It was also not beyond the bounds of possibility that some intercurrent disease such as acute appendicitis had occurred. In any case, she did not seem to be a suitable candidate for surgical exploration and it was decided to give her, in addition to other treatments she was receiving, the best peritonitis medicine that we have at the present, intravenous aureomycin. Mark you, we were not treating a diagnosis here. We were treating a patient, and in conditions of this sort the temptation—and I think it cannot be withstood—is to fire all the guns in the turret at once, and they all went off with appropriate explosions. She had one spike of fever immediately following the aureomycin injection, accompanied by a mild chill, which was otherwise unexplained. Her white count fell. Today for the first time her belly is soft. The rigidity of her neck is now markedly less.

It is apparent that when one encounters meningitis as a clinical disease one does not always follow the schematic outline that we presented in our little textbook introduction.

Other bacterial meningitides have now become more common, actually, than meningococcal meningitis, which used to be the classic type, and I would like to speak again about the necessity of precise bacteriologic diagnosis, particularly nowadays, for this reason. It must be remembered that, particularly when one is dealing with gram-negative meningitides, the treatment will be wholly different. I shall not discuss these, but I should like to comment on two other varieties of bacterial meningitis caused by gram-positive pyogens, the pneumococcus and the hemolytic streptococcus.

Pneumococcal meningitis formerly was a disease carrying a 100 per cent case fatality rate. The principles of pneumococcal meningitis treatment are similar to those of maximally severe meningococcal meningitis: In other words, the establishment and maintenance of high sulfadiazine levels, the use of large doses of aqueous penicillin at three-hour intervals intramuscu-

larly, the initial lumbar puncture with replacement of 10,000 to 20,000 units penicillin in the fluid, the repetition of lumbar puncture in the early stages at twelve-hour intervals, the maintenance of daily lumbar puncture with treatment for probably the first week, and the continuance of some form of treatment, either sulfonamide or penicillin or both, for approximately three weeks. I say this because it is our experience that in pneumococcal meningitis there is a strong tendency to recurrence. You will find that the question of intrathecal penicillin is debated in the literature and perhaps I am reactionary in advising you to use it, but since 1945 in the Presbyterian Hospital we have had eleven cases of pneumococcal meningitis treated on this regimen. Of these eleven cases 100 per cent have survived and until someone comes out with better figures than these I am going to continue to use intrathecal penicillin. Unlike meningococcal meningitis, pneumococcal meningitis is not what one calls a primary type of meningitis. It is almost invariably secondary. It is secondary to otitic conditions. It is also secondary to fractures, particularly at the base of the skull. It is occasionally secondary to remote pneumococcal infections such as pneumonia.

Owing to the frequency with which pneumococcal meningitis is related to otitic infections, it is in my mind of paramount importance that a coordinated attack be made by the internist and the otologist. For that reason I have asked Dr. Fowler to give us his conceptions of the otologist's role in pneumococcal meningitis. Incidentally, before turning the floor over to him, I should like to add that, although hemolytic streptococcus meningitis is perhaps not quite as dangerous as pneumococcus, the management is the same.

DR. EDMUND P. FOWLER, JR.: As Dr. Kneeland has told you, the incidence and treatment of meningococcal meningitis has improved a great deal in the last few years. Similarly, the death rate and complications from other types of meningitis, notably those due to streptococci, pneumococci and influenza B are reduced. These diseases are still with us, however, and are not always properly handled.

The problem in the gram-positive meningitides starts, for the otologist, when inadequate therapy is given or when antibiotics and chemotherapy are given before cultures are taken. We know that streptococcal and pneumococcal meningitis usually come from the ear but with chemo-

therapy the middle ear involvement may be masked while the infection lingers in the mastoid. This is very largely due to anatomic facts concerning which I would like to remind you. There is a great deal of vascularization along the Eustachian tube and both sulfonamides and penicillin are effective in infections of the Eustachian tube, with quite early drainage and disappearance of the pus that develops in the middle ear. But, unfortunately, otitis media is not an infection of a cavity 12 mm. high and 3 mm. deep and 9 mm. across, as one would gather from the words "otitis media." Every middle ear is connected with labyrinthian pneumatic spaces which may go into the petrous pyramid, along the Eustachian tube and down into the mastoid. These pneumatic areas are spaces which have displaced marrow, and some of the connections between them are very narrow. When infection occurs in these spaces the exudate develops into an abscess cavity and there may be very little if any vascularization of the area that is being treated systemically by an antibiotic or sulfonamide. We are often therefore faced in meningitis with a person who has had the symptoms that Dr. Kneeland has so carefully described and perhaps a report showing gram-positive bacteria, either in a smear or in a culture, but when we examine the middle ear we find that the drum looks perfectly normal. The patient will often, at first, do as well as patients usually do with meningococcic meningitis and then one, two, three weeks, or even one, two or three months later there will be a recurrence of the disease. The reason for the failure of therapy is very clear in the autopsies that have been performed in these cases. The middle ear may be almost clear but there will be a breaking down of bone and abscess formation somewhere else. The break-through from one of these abscesses to the meninges is either through the internal auditory meatus where an infected cell has developed very close to a thinned wall of the meatus or through the posterior wall of the petrous pyramid. Rarely is it through the roof of the middle ear or anteromedial to the lateral sinuses.

All my cases of otitic meningitis with gram-positive organisms in the spinal fluid have had, in addition to an inflammation in the mastoid, inflammation in the petrous pyramid. There are very few who do not have marked pneumatization of the petrous pyramid. Under these circumstances one is much more likely to get

meningitis than if there are a small number of cells which are connected to the middle ear and which can easily be drained by myringotomy or when the Eustachian tube is cleared by antibiotics.

Meningitis may develop from acute and chronic otitis media. Acute otitis media most often is due to hemolytic streptococcus or pneumococcus infection, particularly pneumococcus type III. Of 437 consecutive cases of otitis media 137 were found to be due to hemolytic streptococcus and 90 to pneumococci, of which over half were pneumococcus type III. The reason I emphasize this is that the pneumococcus type III organism is slow growing in the middle ear and therefore does not produce pain and rarely much redness. If a patient is comatose you very often do not know that he has an otitis media.

It is now commonly stated by otologists that chemotherapy has made all otitis media as difficult to diagnose and prognosticate as pneumococcus type III infection was in the days before antibiotics. We do not know whether the infection will reappear when sulfonamide or penicillin therapy is stopped. It should be recognized that because of the relatively poor vascularization of mastoid cells it is essential to continue administration of sulfonamides or penicillin in otitis media for a longer period than for pneumonia or other diseases in which antibacterial agents can reach the organisms more easily.

We have been talking principally about acute otitis media and the fairly rapid breaking through of a fulminating process in the middle ear and the mastoid into the meninges. More than half of the cases of meningitis will show a history of previous otitis. I think the history of otitis or even of an earache is perhaps the most important thing to elicit from the patient in this type of case; first, because of the points that I have already emphasized, and secondly, because of the fact that with each otitis media there is a growth of bone which narrows down the connections between the various cells so that when an infection occurs in all the cells it is less likely to drain after myringotomy through the Eustachian tube. The sulfonamides and penicillin are not effective without drainage if there is pus in a free cavity.

Quite a high percentage of meningitis cases occur with recurrent acute otitis media or chronic otitis media when a barrier of bone



between the infection and its possible drainage points has developed over a period of years. It may be that some of these cases are also due to the fact that the pneumatic spaces about on marrow so that a true osteomyelitis may develop. Pathologic sections prove that recurrent otitis media is often due to a flare-up of a low grade chronic osteomyelitis in the petrous bone, very similar to the flare-up in chronic osteomyelitis elsewhere in the body.

Cholesteatoma may also predispose to recurrent otitis media. Cholesteatoma is a growth of skin from the external canal into the middle ear through a marginal perforation. This acts as a foreign body. It also may block off the mastoid from middle ear drainage, break into the labyrinthian cavities and produce a labyrinthitis which gets into the meninges and causes meningitis. Cholesteatomas may break through to the tegumen and involve the meninges directly, and can produce a brain abscess which again may rupture and produce meningitis.

Dr. Kneeland mentioned fractured skulls. I would like to emphasize one point about fractures of the skull which is not generally known, that if a fracture of the skull occurs through the petrous portion of the temporal bone most of the fracture never heals. Therefore, if otitis media develops in a person who has had a fractured skull, even twenty years after the fracture there is an almost wide-open highway into the meninges.

X-rays of the mastoids are always necessary because one may unearth a petrositis or some abscess deep in the temporal bone which is responsible for the meningitis. If this is present, chemotherapy and antibiotics probably will not be sufficient to stop the process permanently and mastoidectomy or perhaps exploration of the petrous pyramid will have to be carried out when the patient's condition permits.

In conclusion, then, otitis media is the usual cause of streptococcal and pneumococcal meningitis. The sulfonamides and antibiotics arrest the disease in the middle ear and meninges but often do not affect the abscess deep within the temporal bone which is the real focus for the meningeal infection. Those abscesses must be attacked surgically, as a rule, or recurrence of the meningitis with cessation of chemotherapy may occur.

DR. KNEELAND: I am afraid that we have given an unduly sanguine and optimistic point of view in this clinic up to now. For that reason

I thought it would be appropriate at this juncture to introduce the customary gloomy note. Therefore, I have asked Dr. Stearns to discuss his experience in the treatment of tuberculous meningitis.

DR. WILLIAM H. STEARNS: I envy Dr. Kneeland his chance to exhibit some complacency in discussing results of the present treatment of meningococcal meningitis. No such opportunity is afforded one who has to discuss tuberculous meningitis, particularly as it occurs in the adult. It is true that the disease has been almost uniformly fatal in the past and that since the advent of streptomycin remissions of several months have been obtained in a fair proportion of cases, with apparent "cures" of two or three years or more in a few; but results of treatment can hardly be called satisfactory.

The most encouraging results have been obtained in infants and children, and I might mention especially the series treated under the direction of Dr. Edith Lincoln on the Children's Tuberculosis Service of Bellevue Hospital. She has a group of twenty-two cases of tuberculous meningitis, most of them followed for nearly two years and a few for longer. Of those twenty-two children and infants, six have died and sixteen are still living three hundred days or more after the beginning of treatment. Nine of the sixteen are alive more than a year and a half after the start of treatment, and three of them more than two years and a half. In this series promizole was given by mouth in addition to streptomycin intramuscularly and intrathecally.

A larger study under the auspices of the U.S. Public Health Service is now in progress in a number of hospitals in an effort to evaluate further the important factors in treatment of tuberculous meningitis in children. Figures are not yet available for publication but it may be said that, thus far, results have not been quite as good as in Dr. Lincoln's series. Whether this represents the difference in the proportion of cases classified as "minimal" and "advanced" at the time of diagnosis, or a difference in the dosage of the drugs in the two series remains to be determined.

When one considers tuberculous meningitis in the adult, results of treatment with streptomycin are seen to be far less encouraging. Probably the most informative analyses of the situation in this country are those based on data provided by the Veterans Administration Hospital for tabulation in their central office in Washington.



In their first series of one hundred cases of miliary tuberculosis and/or meningitis treated with streptomycin, eleven of nineteen patients who had miliary tuberculosis without meningitis are reported living after two years. This is in contrast to thirteen patients who had miliary tuberculosis followed by meningitis. All thirteen of those were dead at the end of two years. Of twenty-five patients who had both miliary tuberculosis and tuberculous meningitis when treatment was begun only one was reported living after two years. Of the meningitis cases, results were best in the group who had meningitis without miliary tuberculosis; seven of forty-three patients in this group have been reported living after two years. Their figures, I think, are fairly representative of results of treatment in this country.

More recently para-aminosalicylic acid and promizole have both been used as adjuvants to streptomycin in an effort to better the results. Again referring to the tabulations of the Veterans Administration, no particular improvement is noticeable as yet.

Diagnosis of tuberculous meningitis in an early stage is not always easy. Symptoms may be extremely vague and signs of meningeal irritation minimal or absent for some time. Even with well developed signs of meningitis it may be difficult or impossible to demonstrate the etiologic diagnosis promptly. Spinal fluid findings of increased cells (predominantly lymphocytes), increased protein, and low sugar are suggestive but not conclusive. The level of the spinal fluid chlorides has not been particularly helpful in our experience. In the event of failure to demonstrate acid-fast bacilli in the spinal fluid, decision as to treatment may be based on other factors, including the patient's general condition and the presence of tuberculosis elsewhere in the body. In a number of cases we have been able to establish the diagnosis bacteriologically only after a relapse has occurred.

It is obvious that in a patient with miliary tuberculosis a diagnosis of tuberculous meningitis may be made with much more assurance, on the basis of equivocal spinal fluid findings, than will be the case in a patient without evidence of manifest tuberculosis elsewhere. If it is made a practice to examine the spinal fluid as soon as a diagnosis of acute miliary tuberculosis is made or suspected, and every week or two thereafter, meningitis may be discovered in

many instances before the development of definite symptoms or signs.

In patients with pulmonary or other forms of tuberculosis a spinal tap should be made at the earliest sign of meningeal irritation. On occasion it may be indicated simply because of such non-specific signs as vague personality changes occurring under observations. There should be a high index of suspicion particularly in cases with extrapulmonary hematogenous foci.

The difficulty of establishing a definite bacteriologic diagnosis early in tuberculous meningitis, and the desirability of starting treatment as soon as possible, put a heavy responsibility on the clinician now that the infection can be at least arrested in a certain number of cases. The need for certainty lies in the long continued treatment and its possible harmful effects. In doubtful cases I believe it is proper to withhold treatment while observing the patient closely and getting daily determinations of the sugar, cells and protein in the spinal fluid. A number of cultures for tubercle bacilli should be made in addition to smears for acid-fast bacilli. Even though the cultures will not be reported soon enough to influence the decision as to treatment, it is reassuring to have a positive report later on in the event that treatment was initiated in a case about which there might be some lingering doubt. This problem is a real one, especially in patients without evidence of tuberculosis in the lungs or elsewhere. It seems inevitable that a certain number of cases of benign lymphocytic choriomeningitis may be included as "cures" in series in which all diagnoses were not substantiated bacteriologically.

At the present time I doubt that anyone has very strong convictions as to the one best regimen of treatment of tuberculous meningitis in the adult. It is generally agreed that early diagnosis and treatment are important but there is no uniformity of opinion beyond that point. Suggested regimens vary with respect to duration of treatment, dosage, mode of administration and even the type of streptomycin to be used. Much of the confusion probably arises from the fact that some apparently good results have been obtained with all regimens, even those of relatively short duration and low dosage of streptomycin. This is not to be taken as evidence that such a regimen is to be preferred; rather it may be taken to indicate that the character and size of the disseminating focus is

the determining factor. Occasionally a relatively short course of streptomycin may be sufficient to allow such a focus to heal but more often even a course of three or four months has ended in failure.

Since lasting remissions have been obtained in only a small proportion of cases of tuberculous meningitis in the adult, it would seem reasonable to use even longer courses of treatment than has been the custom here in the hope that the disseminating focus may heal if bacterial activity can be suppressed sufficiently long. The weight of evidence from European reports, which claim considerably better results than we have obtained, favors continuation of treatment for from six to twelve months.

The importance of intrathecal administration of streptomycin is still subject to investigation. At one extreme are those who believe that intrathecal treatment should be given as long as possible; at the other are those who believe that comparable results may be obtained with intramuscular injections only. The feasibility of treating tuberculous meningitis without giving streptomycin intrathecally has been under study at Fitzsimmons General Hospital. As you know, there is very slight secretion of streptomycin into the spinal fluid when the meninges are normal, but with inflammatory changes significant amounts may be found there. Investigators at Fitzsimmons General Hospital have shown that a rise of the streptomycin level in the spinal fluid to 10 micrograms or more, in patients who are receiving streptomycin intramuscularly, may be taken as an indication of developing meningitis. They have obtained an average of almost 30 micrograms/cc. in patients with tuberculous meningitis without any intrathecal treatment. If it could be established that intrathecal treatment is not necessary, there would be obvious advantages, among them freedom from the irritating effects of streptomycin given into the spinal canal.

It has been our custom to give 2 gm. of streptomycin intramuscularly daily for ninety days and 20 intrathecal injections of 50 mg. each.

The intrathecal injections have been made daily for three days, then three times a week. In the last few months we have given para-aminosalicylic acid by mouth as well, in the hope of deferring bacterial resistance to streptomycin. This is rather a middle of the road regimen and

has met with only average success. It is planned to prolong the period of intramuscular treatment and of para-aminosalicylic acid to at least six months. Probably we will increase the number of intrathecal injections, though at this time we do not know how important this may be.

It probably should be mentioned that the status of dihydrostreptomycin, particularly when given intrathecally, has been questioned by some. There seems little doubt that certain lots of this form of streptomycin were more irritating than regular streptomycin when given intrathecally, and that a higher incidence of impaired hearing was associated with it even when given by the intramuscular route only. More recently there is reason to believe that these drawbacks have been overcome. If so, there is advantage in its use when 2 gm. of the drug are to be given daily for any prolonged period for it seems definitely less toxic to the vestibular apparatus than regular streptomycin in equal dosage.

Finally, there remains the problem of the fibrinous adhesions which are apt to occur in tuberculous meningitis and are a cause of internal hydrocephalus and of death in a certain number of cases. Streptokinase is under investigation in England, in some instances being used for prevention of block. Here it has been tried in a few cases after block has occurred, with some quite severe reactions. Its usefulness and safety for this purpose remains to be determined.

In closing, it is quite evident that results of treatment of tuberculous meningitis in the adult are far from satisfactory, and that no single regimen of treatment can be recommended as the best. However, there are many patients alive and well who would have been dead long since without streptomycin. There is every reason to believe that, in time, the problem can be solved.

**DR. KNEELAND:** Dr. Stearns has struck a suitably somber note here but in spite of his gloom an occasional patient of his does survive. Such a patient is very likely to come into Dr. Fowler's hands after successful treatment of his tuberculous meningitis, and I should like Dr. Fowler to say a few words, if he will do so, on the management of the complications of streptomycin therapy.

**DR. FOWLER:** As you know, streptomycin has a peculiar affinity for the eighth nerve. Strangely, dihydrostreptomycin seems to have more affinity for the acoustic division while ordinary strepto-



mycin has particular affinity for the vestibular division. Intrathecally, dihydrostreptomycin is more likely to produce deafness than is ordinary streptomycin. I have seen three cases, one who had only a single dose intrathecally and has total deafness, and another who had one or two doses intrathecally. I think all the drug houses now advise against the use of dihydrostreptomycin intrathecally. One must be very cautious about blaming the deafness or vestibular troubles on streptomycin. More often these symptoms come from the meningitis and not from the drug. When we were working on streptomycin in influenzal meningitis, we found that total deafness and total vestibular loss was nearly as high as when no streptomycin had been given.

This is a very important point, i.e., meningitis does produce deafness. As Dr. Kneeland says, the infection of the meninges runs along the nerves that emerge from the cranial cavity so, of course, it may run along the acoustic nerve and produce labyrinthitis. Sometimes, therefore, it produces deafness on the opposite side from the ear that originally caused the trouble. The highest percentage of acquired deafness in the schools for the deaf is from meningitis. Fortunately, we have now learned a great deal about rehabilitation of deafness and vestibular disorders. If a patient is young, within a remarkably short time he compensates for his vestibular loss by the use of his eyes and the vestibular spinal system. The deafness, unfortunately, is a little more difficult to rehabilitate because invasion of the labyrinth usually destroys the hearing so completely that there are rarely more than a few islands left; but with lip reading and auditory training and with the use of a hearing aid, which is used primarily for feel, warning and for rhythm of speech, many of these patients do well.

I would like to cite one patient who had meningococcic meningitis while serving with the ski troops. He was high in the mountains on bivouac. He became ill. He was finally brought into a station hospital for a short time. They thought he had measles because he had a slight rash. After six days he was taken to a general hospital where he stayed for three days before lumbar puncture was done. At that time his hearing had completely gone. Finally he recovered completely except for his hearing and his vestibular apparatus and for his psyche. For

a nineteen year old boy suddenly to go completely deaf with no communication with the world, and a skier who cannot even walk straight on the hospital floor, the reactions of meningitis are a tremendous shock. This boy very quickly learned to walk on the flat, but I picked him up fifteen times between my house and a nearby house when we walked through the woods one dark night. I practically had to carry him because he could not use his eyes. That boy learned to use the hearing aid, learned to lip read, graduated summa cum laude from Yale, and is now skiing a lot better than I do.

DR. KNEELAND: Dr. Loeb, would you now tell us about the use of adrenal cortical material in the Waterhouse-Friderichsen syndrome?

DR. ROBERT F. LOEB: I would like to agree with Dr. Kneeland. I think the fundamental difficulty in the Waterhouse-Friderichsen syndrome is related to severe peripheral circulatory failure as the result of infection. In two patients with that syndrome Dr. Cosgriff found the serum sodium to be low, the blood sugar was low and the NPN was high. These changes are compatible with adrenal insufficiency, though not specific. Since we know that the adrenal gland is damaged also to a varying degree in this syndrome, I think it is proper that supportive adrenal therapy should be employed as an adjuvant. But I agree fully with Dr. Kneeland that the problem is primarily one of treatment of peripheral circulatory collapse on the probable basis of a bacterial toxin.

DR. COUNT D. GIBSON, JR.: There is one item about streptokinase. Dr. Tillett has treated four patients with acute purulent meningitis who had a block of their cisternal system and in each case the block was dissolved within a matter of four hours after injection of the enzymes. The experience is much more disappointing with tuberculous meningitis but I think this form of therapy should be kept in mind.

DR. KNEELAND: I think yours is an important addition, Dr. Gibson, because block in the circulation of cerebrospinal fluid is one of the most difficult problems we are called upon to face in meningitis.

STUDENT: What about virus meningitis?

DR. KNEELAND: That is a terribly complicated situation. There is no specific therapy for virus meningitis (if we exclude the very rare case of lymphogranuloma venereum) and yet diagnosis is important from the standpoint of prognosis,



long-term management and epidemiology. Unfortunately, specific etiologic diagnosis involves the services of a fully equipped virus laboratory, of which only a few exist, and is usually retrospective in character, i.e., it is made by serologic means during convalescence.

It is remarkable, when one comes to think of it, how few purely neurotropic virus diseases there are which are peculiar to man. Poliomyelitis, of course, comes first to mind, and here in the paralytic cases the diagnosis is clinical. Von Economo's encephalitis is largely of historical interest but one does see a certain amount of "inclusion encephalitis" which is presumably viral in origin but of which little is known. The rest of the human viruses which can cause meningoencephalitis are primarily pathogenic for other tissues such as mumps, infectious mononucleosis, measles, etc. Some of this group such as measles, varicella, etc., produce demyelinating lesions and it is questionable if virus can be demonstrated in central nervous tissue.

On the other hand, there are a considerable group of animal viruses which, often by means of an insect vector, may infect man and give rise to meningoencephalitis. In this group are rabies, to begin with, and then the arthropod-borne diseases such as equine encephalomyelitis, and the St. Louis, Japanese B, Russian Spring-Summer, etc. types of encephalomyelitis. Lymphocytic choriomeningitis should also be mentioned here.

All these viruses produce a meningeal reaction with a varying encephalitic component. Spinal fluid cell counts tend to be fairly low with the cell type predominantly lymphocytic. The sugar is not reduced. At the bedside the most important thing is to distinguish them from the bacterial meningitides which are susceptible to therapy.

The newer antibiotics such as aureomycin and terramycin are not effective against neurotropic viruses in the laboratory. It is doubtful whether they influence any of the neurotropic virus diseases in man in which they have been tried. However, as mentioned earlier, the virus of lymphogranuloma venereum is susceptible to their action and this may occasionally cause meningoencephalitis in man. In regard to their effect on herpes, the evidence is equivocal. In all likelihood they do no harm and are, therefore, often used in the herpes types of meningoencephalitis.

## SUMMARY

**DR. FREDERICK K. HEATH:** The key to good management of meningitis is early suspicion of its presence. Prompt lumbar puncture with smear, culture, differential cell count, sugar and protein determinations on the spinal fluid should precede therapy and open the door to correct diagnosis and adequate treatment. Close attention to the patient until recovery pays dividends.

Meningococcal meningitis responds well to high blood levels of sulfadiazine alone but in more severe cases intramuscular penicillin should be added. Intrathecal penicillin is required only in critical situations. Repeated spinal puncture is reserved for complicated severe cases. Cisternal block may respond to intrathecal streptokinase. Peripheral circulatory failure is a feature of severe infections demanding the entire gamut of antibacterial agents plus whole blood and supportive adrenal cortical agents.

Pneumococcal meningitis is almost uniformly secondary to disease in the ear, less often to a pneumococcal focus elsewhere, and rarely follows basal skull fractures. Treatment consists of intensive and prolonged sulfadiazine, intramuscular and intrathecal penicillin, otologic measures as indicated, and streptokinase for blockage.

Streptococcal meningitis may be regarded as similar to the pneumococcal disease.

Tuberculous meningitis still does not do well despite long courses of streptomycin alone or plus the addition of promizole or para-aminosalicylic acid. The most favorable situation would seem to exist when miliary tuberculosis does not coexist.

Meningitis of viral origin has no specific therapy, unfortunately, except in rare instances of lymphogranuloma venereum and possibly herpes which may respond to aureomycin or terramycin.

Deafness and vestibular disturbances are common sequelae of all types of meningitis or its therapy. Special training is important to rehabilitate patients adequately with these complications.

Not mentioned in this clinic were the gram-negative meningitides nor those due to yeasts. *B. influenzae* is the most common of the former and is chiefly a problem in pediatric practice; there is no specific therapy of proven value for the latter.

# Clinico-pathologic Conference

## Convulsions and Multiple Thrombophlebitis

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. D., (No. 188750), was a white married housewife, eighteen years of age, who was admitted to the Barnes Hospital on September 7, 1950, because of convulsions. The patient was too ill to give her own history and the information was obtained from her husband; he was considered reliable. The family history was irrelevant. The past history was of interest in that the patient had not had mumps or chicken pox and she had not been exposed recently to either of them. No other significant illnesses had occurred. She had never suffered trauma to the head and there was no past history of convulsions. She lived with her husband on a farm where the usual domestic animals were kept; none had had any apparent illness.

One month before admission the patient had a spontaneous abortion in the seventh month of pregnancy without evident complications. Two weeks before entry she developed a mild upper respiratory infection described as a "cold"; one week later she complained of generalized aching, frontal headache, which was worse on the right side, and nausea and vomiting. The week before she was admitted her headache became more intense and vomiting persisted; five days prior to entry her temperature was found to be normal. At that time she was admitted to a hospital in a nearby community and was given demerol for headache. The following day she became semicomatose. Neurologic examination was said to have been negative as were also a routine blood count and urinalysis. A lumbar puncture was performed; the fluid showed "slightly increased pressure," 7 cells, a negative Pandy test, and negative Kahn and colloidal gold reactions. One day before she was admitted to the Barnes Hospital she was said to have had negative general physical and neurologic examinations. Because she had developed a low grade fever she was given both sulfonamide and streptomycin. She was transferred to the

Barnes Hospital because she became comatose and developed repeated generalized convulsions.

At the time of entry physical examination revealed a temperature of 38.5°C., pulse 120, respirations 20 and blood pressure 120/80. When first seen the patient was having clonic convulsions which were bilateral but more marked on the right; her head and eyes turned to the right. The convulsions occurred repeatedly, each episode lasting several minutes and being followed by a three-minute interval during which the patient was quiet. She was given intravenous sodium amytal which controlled the convulsions and permitted examination. The patient appeared to be dehydrated. The pupils were dilated and equal and the fundi were entirely normal. Examination of the upper respiratory tract was negative. There was no generalized glandular enlargement. The lungs were clear to percussion and auscultation, and the heart revealed no abnormalities except for tachycardia. Abdominal examination was negative; pelvic examination was deferred. A complete neurologic examination revealed only hypoaactive deep tendon reflexes.

The laboratory data were as follows: *Blood count*: red cells, 4,810,000; hemoglobin, 13.7 gm.; white cells, 13,850; differential count: basophils, 1 per cent; segmented forms, 84 per cent; lymphocytes 5 per cent; monocytes, 10 per cent. *Urinalysis*: albumin, trace; sugar, 2+; acetone, 1+; sediment, negative; culture, negative. *Stool examination*: guaiac positive (trace). *Blood Kahn test*: negative. *Non-protein nitrogen*, 25 mg. per cent.

Shortly after admission the patient was subjected to lumbar puncture. The initial pressure was 300 mm. of water, and the final pressure 145 mm. of water. The fluid was clear, containing only 2 cells per cubic mm. Spinal fluid protein and sugar were normal, and the colloidal gold and Wassermann reactions were negative. Culture of the fluid was negative.



On the day following entry the patient thrashed about aimlessly, occasionally screaming and moaning. During the first twenty-four hours she received large amounts of fluid intravenously and subcutaneously and her hydration was much improved. She remained comatose and had frequent clonic movements of the extremities, the head turning in both directions. Roentgenograms of the chest were negative; those of the skull showed only hyperostosis frontalis interna. The patient was given thiantoin, sodium phenobarbital and antibiotics; in addition, cortisone in a dose of 100 mg. three times daily was begun. Tube feedings were instituted.

By the third hospital day the white blood cell count had fallen to 7,400 with 9 per cent stab forms and 74 per cent segmented forms. Lumbar puncture was repeated and revealed an initial pressure of 285 mm. of water and a final pressure of 110 mm. of water. The fluid was again within normal limits in all respects.

On the fourth hospital day the patient's temperature was 38.7°C. and the pulse rate 152. She was still comatose but convulsions occurred less often. Neurologic examination revealed ankle clonus on the right but no plantar response on that side. A positive Babinski sign was elicited on the left. During the next several days her condition was essentially unchanged. Another lumbar puncture revealed only a 2+ Pandy test. A Schwartz-Watson test was negative.

At the end of the first week the patient was still comatose; she continued to scream intermittently but no longer exhibited clonic movements. Further studies at this time revealed the blood calcium to be 9.9 mg. per cent, phosphorus 2.9 mg. per cent and alkaline phosphatase 1.4 Bodansky units. The red blood cell count was 3,530,000 with 10.4 gm. of hemoglobin. The temperature gradually fell and during the second week never went above 37.8°C. Convulsions ceased completely but the patient remained lethargic. The neurologic examination continued to be essentially negative. Cortisone dosage was decreased to 100 mg. daily. At the end of the second week the patient uttered a few intelligible words. Complement fixation tests on blood obtained at the time of the patient's entry were negative for mumps, Western equine encephalitis, St. Louis encephalitis, and lymphocytic choriomeningitis; the heterophile agglutination test was also negative.

The patient became conscious and oriented.

The only abnormal neurologic finding was her inability to move the left arm. A number of liver function tests was negative except for the prothrombin time which was 43 per cent of normal. Early in the third week after the patient had shown marked improvement, she had two transient left-sided clonic convulsions and her temperature, which had been normal, rose to 38.8°C. Laboratory studies at this time revealed persistence of mild anemia and a leukocytosis of 20,300 with 2 stab forms and 73 segmented forms. The blood indices were normal, the prothrombin time was 54 per cent of normal, blood chlorides 88 mEq./L. and CO<sub>2</sub> combining power 30.1 mEq./L. On the seventeenth hospital day the patient again had transient left-sided convulsions and she was given dilantin. The leukocytosis persisted and a few rales were heard at the lung bases. Repeat x-ray examination of the chest revealed elevation of the right diaphragm and diffuse clouding of the right lung field, interpreted as pneumonitis. Antibiotic therapy which had been discontinued was resumed. The complement fixation tests were repeated with the following results: Western equine encephalitis, positive 1 to 256 (Table 1); St. Louis encephalitis, positive 1 to 32. Heterophile antibodies were present in a dilution of 1 to 7.

The patient remained free of seizures, was oriented and cerebrated well. The only neurologic findings of interest were slight nystagmus on left gaze and weakness of the left arm.

Three weeks after admission the patient developed right supraclavicular lymphadenopathy with extreme tenderness, swelling and redness in that area. Her temperature, which had been normal, rose to 37.8°C. Another chest film revealed signs suggestive of a right pleural effusion. Pain in the right supraclavicular region became marked and a right stellate ganglion block was done. The pain decreased and the patient was able to move her neck. On the twenty-third hospital day her temperature reached 38.5°C. The right biceps area became tender and a cord-like vein could be palpated there. A similar finding was noted in the right supraclavicular region. On the following day thrombophlebitis of the brachial, axillary and external jugular veins on the right was apparent. All of these vessels could be felt as thick tender cords. On the twenty-fourth day the clotting time was 5 minutes, and 200 mg. of depo-heparin were given. The following day the clotting time was 9



minutes and the same dose of depo-heparin was repeated. On the twenty-fifth day the patient was improved both subjectively and objectively. Dullness over the right lower lobe decreased, but a friction rub was heard at the extreme right base. The clotting time was 42 minutes and 100 mg. of depo-heparin were given. Following this dose the clotting time reached 120 minutes and heparin was withheld.

At the end of the fourth week the patient still had a low grade fever and the signs in the chest were unchanged from those previously noted, but the signs of thrombophlebitis were subsiding. At this time pelvic examination was performed and was negative. Heparin was given as indicated and the patient improved. Slight weakness of the left arm was the only neurologic abnormality. On the thirty-first hospital day the patient became afebrile and appeared further improved. Complement fixation tests at this time revealed titers of 1 to 256 for Western equine encephalitis, and 1 to 16 for St. Louis encephalitis.

Another chest x-ray was obtained which demonstrated reduction in the amount of fluid in the right chest but persistent elevation of the right leaf of the diaphragm. The patient had continued to improve, and at the end of the fifth week she felt well enough for arrangements to be made for physiotherapy to her left arm. The signs of thrombophlebitis had subsided and her blood count was normal.

On October 21, 1950, the forty-fifth hospital day, the patient suddenly became weak while walking to the bathroom. She perspired profusely, vomited and collapsed. Her pulse and blood pressure were unobtainable; the heart rate was 140 and respirations were 36 per minute. She thrashed about in bed frothing at the mouth and shortly thereafter expired.

DR. HARRY L. ALEXANDER: The protocol records a particularly tragic illness. This patient was admitted to the hospital in critical condition, presumably suffering from encephalitis. Subsequently after she appeared to be making a satisfactory recovery, she developed evidence of multiple, severe thrombophlebitis. This process likewise seemed to be subsiding when the patient died suddenly and unexpectedly. To consider first the diagnosis of encephalitis, it is well to point out that differential diagnosis on clinical grounds may be difficult or impossible. Among those to be considered in this case are St. Louis, Western equine, post-infectious, von

Economo's and "idiopathic" forms of encephalitis; this list is by no means complete but affords a point of departure for the discussion. Dr. Harford, do any of the so-called post-infectious encephalitides represent actual infection of the central nervous system by virus?

DR. CARL G. HARFORD: The encephalitis which follows mumps probably does since the virus has been isolated from the spinal fluid under such circumstances.

DR. ALEXANDER: I am told that a diagnosis of Western equine encephalitis was made by Dr. Levy when he saw this patient in consultation. Would you tell us why you made that diagnosis, Dr. Levy.

DR. IRWIN LEVY: We were not able to make an unequivocal diagnosis of Western equine encephalitis, but at the time this patient was in the hospital we were seeing about six other patients with encephalitis which was thought to be due to the Western equine virus. In a number of them positive complement fixation tests had been obtained, and it was for this reason that the presumptive diagnosis was made in this particular case.

DR. ALEXANDER: From a clinical standpoint were this patient's findings typical of any specific type of encephalitis?

DR. LEVY: No, I do not believe that they were. As you indicated, the clinical differentiation of the encephalitides is very difficult. We are dependent on laboratory confirmation.

DR. ALEXANDER: Is it possible, Dr. Moore, for the pathologist to differentiate the lesions of one form of encephalitis from those of other types?

DR. ROBERT A. MOORE: I believe that St. Louis encephalitis can be separated with reasonable certainty from the equine and post-infectious forms.

DR. ALEXANDER: Dr. Levy's diagnosis of Western equine encephalitis was apparently confirmed by complement fixation tests. The test on acute phase serum was reported as negative whereas that on convalescent serum was positive. Dr. Harford, will you comment on this particular laboratory procedure in regard to specificity and validity?

DR. HARFORD: In the diagnostic laboratory of the hospital we have performed complement fixation tests for various viral diseases, among them the viral encephalitides. This procedure in the case of the neurotropic viruses is complicated by the fact that the antigens are prepared from

brain tissue which contains a large amount of lipid. These antigens are often somewhat anti-complementary so that it is more difficult to carry out reliable tests. Our results in this case are shown in Table 1. The high titer of the complement fixation test performed on the convalescent serum surprised us, and it was considered desirable therefore to check the results by the more reliable mouse neutralization test. Employing that procedure both acute phase and convalescent sera gave negative results. Also in order to perform a complement fixation test of greater precision, we employed the method used by Dr. Bukantz in which a 50 per cent hemolytic unit is determined.<sup>1</sup> Again, with this procedure both acute phase and convalescent sera were negative. It is important to note that antibodies in these diseases are relatively less stable than most other antibodies so that sera for these tests should be preserved in the frozen state. This precaution was carried out in the present case. Isolation of the virus from the spinal fluid in St. Louis or Western equine encephalitis is extremely rare. We did, however, inject mice by the intracerebral route with spinal fluid from this patient with negative results. As a result of our studies we would be unable to confirm the clinical diagnosis of Western equine or St. Louis encephalitis.

DR. LEVY: I should like to mention that in our patient who had a complement fixation titer for Western equine encephalitis over 3,000 the mouse neutralization test was also positive. I would like, therefore, to ask Dr. Harford why he considered the titer of 350 in this case so surprising.

DR. HARFORD: We were suspicious of the validity of such high titers in both instances because they are far beyond those usually obtained with strongly positive sera.

DR. ALEXANDER: Dr. Levy, are you willing to accept the possibility that this patient did not have Western equine encephalitis?

DR. LEVY: I would certainly agree that on the basis of laboratory findings one could not be certain of the diagnosis. In regard to St. Louis encephalitis I would like to ask Dr. Margaret Smith, who has worked extensively with the St. Louis virus, whether there is at present any known disease attributable to it in this area or elsewhere.

DR. MARGARET G. SMITH: There have been

no recent recognized epidemics. About three years ago several patients were seen in whom the diagnosis of St. Louis encephalitis was confirmed by laboratory study, and there have been cases reported recently in California. Throughout the last half of the thirties and the early forties we found a number of cases in children, and almost every summer we were able to identify several sporadic occurrences, but in the last few years none has turned up.

DR. ALEXANDER: In attempting to identify the type of encephalitis which this patient had, Dr. Levy, do you think the fact that she had a respiratory infection one week before entry was of significance? Could she have had post-influenzal or post-infectious encephalitis?

DR. LEVY: That is conceivable. I do not know how a definitive clinical diagnosis could be made.

DR. ALEXANDER: Dr. Wilson, I believe you saw this patient. Why was she given cortisone?

DR. KEITH S. WILSON: We gave it at Dr. Levy's suggestion.

DR. LEVY: In the encephalitides there is evidence of considerable inflammatory reaction involving the brain. It was postulated that a beneficial effect might be obtained from cortisone in terms of suppression of the inflammatory reaction. Our reasoning was empirical.

DR. HARFORD: In regard to the use of cortisone in viral disease of the central nervous system, it should be pointed out that recently Schwartzman has reported that certain strains of poliomyelitis virus which ordinarily produce a very mild disease in hamsters cause universally fatal infections in hamsters given cortisone.<sup>2</sup>

DR. W. BARRY WOOD, JR.: It is also worth pointing out, Dr. Alexander, that when Dr. George Baehr presented his results on the use of cortisone in lupus erythematosus in Atlantic City last year, he described a patient who had epilepsy in addition to lupus. Shortly after cortisone therapy was begun the patient developed status epilepticus and died. At that time he raised the question as to whether it would not be dangerous to use cortisone in patients with convulsive disorders, and on the basis of his experience in that one case, he issued a word of caution. I would like to ask Dr. Levy whether he would agree that epilepsy constitutes a contraindication to the use of either ACTH or cortisone.

<sup>1</sup> KENT, J. F., BUKANTZ, S. C. and REIN, C. R. *J. Immunol.*, 53: 37-50, 1946.

<sup>2</sup> SCHWARTZMAN, G. *Proc. Soc. Exper. Biol. & Med.*, 75: 835, 1950.



DR. LEVY: I have no way of answering that question on the basis of my experience. It may be that the change in electrolyte and water balance could be extremely detrimental in patients with convulsive states. On the other hand, in this patient, I do not believe that cortisone adversely affected the convulsive pattern. Indeed, we were impressed by the fact that she began to improve when cortisone was given. Whether or not that was coincidence I do not know. In regard to cortisone in viral encephalitis it must be remembered that there is evidence, at least under certain circumstances, that encephalomyelitis may arise as a result of hypersensitiveness, and in such instances it has been shown that cortisone may have a beneficial effect.

DR. WOOD: I think that point is well taken; it is supported by experimental evidence compiled by Dr. Kabat.

DR. THOMAS H. HUNTER: It does not seem quite clear to me why the discussion of this patient's disease is limited to encephalitis. Other interesting clinical changes were going on which make me doubt the diagnosis of encephalitis. How, for example, was vascular disease ruled out as a possible underlying cause of the patient's clinical picture? Was the abortion which had occurred shortly before she became ill of any significance? It is sometimes very easy for the clinician to be misled as to the cause of diffuse central nervous system disease.

DR. LEVY: Dr. Hunter's point is a good one. During the first stages of this patient's illness we were actually less concerned with the diagnosis than we were with the attempt to control the convulsions which were at that time the major problem. Actually the diagnosis of encephalitis seemed to evolve rather than to have been put forth immediately on admission. In regard to the possibility of vascular disease it is perfectly true that, for example, an infected embolus might produce secondary convulsions because of concomitant contiguous inflammatory changes. Ordinarily, however, embolic processes do not produce convulsions. There was no evidence that she had pelvic infection. She had apparently been in good health after the abortion until the development of the upper respiratory infection. One would have to consider other forms of vascular involvement including a tumor such as an angioma which could have produced convulsions; with such a tumor, however, one would expect to find blood in the spinal fluid.

Another unusual cause of a clinical pattern such as this patient exhibited might be large areas of softening secondary to multiple sclerosis.

DR. ALEXANDER: Let us consider certain other interesting aspects of this case. As the patient began improving in the second hospital week, her temperature rose and she developed severe pneumonitis which never cleared. The question arises as to whether she had aspiration pneumonia as a complication of tube feedings; the Levine tube was removed, however, almost a week before the signs of pneumonitis appeared. Would you comment on the x-ray films, Dr. Fee?

DR. WESLEY FEE: The initial chest film was made on September 7th. Aside from a calcified lymph node in the left hilar region the chest was clear. About two weeks later, an anteroposterior film was taken with the patient in the supine position. At that time there was generalized haziness over the entire right lung field and a slight increase in the prominence of the lung markings. The left lung was essentially clear. Three days later a postero-anterior film with the patient erect was obtained. At that time the right leaf of the diaphragm was elevated and there was some pleural fluid at the right base. Further, there was definite cardiac enlargement. On October 6th it was again noted that the right leaf of the diaphragm was elevated, that there was a right pleural effusion and that the lung markings were slightly more prominent on the right than on the left. The cardiac size had decreased. About twelve days later the cardiac size had returned to normal but elevation of the right diaphragm and right pleural infusion persisted.

DR. ALEXANDER: Do you have any comments about the films, Dr. Goldman. Do you think that the findings were related in any way to the patient's sudden death later on?

DR. ALFRED GOLDMAN: I am unable to say. The most impressive finding was the elevation of the diaphragm which could have been due either to paralysis of the diaphragm or may have been associated with atelectasis.

DR. ALEXANDER: As the patient appeared to be improving she developed extremely extensive thrombophlebitis. Dr. Wilson, would you comment on this complication.

DR. WILSON: The most dramatic finding initially was the painful area on the right side of the patient's neck, but even before that appeared she had a reaction at the site of an



injection in a vein on the dorsum of the right hand; the area became discolored and somewhat tender. It seemed rather insignificant until the area in the right supraclavicular region was noted. It appeared that the right external jugular vein had become thrombosed, and one could feel obvious thrombosis of other veins of the arm. The patient's hands and arms swelled somewhat but not to the degree that one would have expected had all of the major veins been thrombosed.

DR. ALEXANDER: Why was the stellate ganglion block done?

DR. WILSON: The patient was complaining of pain, often excruciating. Sympathetic block has been used frequently in the treatment of pain and spasm due to thrombophlebitis in the lower extremities, and by analogy we decided that it would be well to try it in this situation. The major beneficial effect was relief of pain.

DR. ALEXANDER: Would you comment on the use of depoheparin, Dr. Harrington.

DR. WILLIAM J. HARRINGTON: We were faced with a rather difficult problem. The patient had a cerebral lesion, and we wanted to avoid inducing bleeding into that lesion. The effect of anticoagulants in patients with encephalitis, specifically in regard to induction of capillary bleeding, is not known. On the other hand, in view of the extensive thrombophlebitis there was no question that anticoagulant therapy was indicated; at that point in her course thrombophlebitis was a more serious risk to the patient than the resolving encephalitis. It was decided, therefore, that heparin was the treatment of choice because its effects could be reversed so promptly. The patient was given heparin as outlined in the protocol; as it turned out, a tragic ending came to a successful therapeutic procedure.

DR. ALEXANDER: At what clotting time should one aim in using heparin?

DR. HARRINGTON: I do not believe that one can state an optimum figure as far as prolongation of the clotting time is concerned. With the methods we use for the determination of clotting time, fifteen minutes is the upper limit of normal and prolongation beyond twenty-five minutes is considered adequate. One need not be as concerned with how long the clotting time is but rather how short it is. Swedish investigators have given heparin intravenously in intermittent doses so that the clotting time becomes infinite, and yet they have not had serious complications.

DR. ALEXANDER: The terminal event was sudden. The patient was up and about and appeared to have come a long way toward regaining normal health when she died. Are there any suggestions about the final episode?

DR. HUNTER: Don't you think that pulmonary embolism is the most likely possibility?

DR. ALEXANDER: I think that is a very likely suggestion, although the interval of two weeks from the subsidence of thrombophlebitis to death seems rather long.

DR. HUNTER: That would not seem unusual to me, Dr. Alexander. In the first place the embolus need not have come from a site which previously showed active thrombophlebitis. As a matter of fact, emboli are much less likely to arise from a site where there is inflammation than they are from unsuspected sites. It seems to me that the important factor here is that the patient demonstrated the tendency to form venous thrombi, and an unsuspected thrombus may have been developing in the period prior to the terminal episode.

DR. ALEXANDER: Are there other comments.

DR. ALBERT I. MENDELOFF: I note the features here in the terminal episode of vomiting, perspiration and tachypnea; they seem to me to be less characteristic of pulmonary embolus than of cerebral embolus or thrombosis. In the few patients I have seen die of pulmonary embolus pain in the chest, difficulty in breathing and irregular gasping were prominent rather than the collapse with rapid heart rate and deep respiration such as this patient had. To me, her

TABLE I  
TESTS FOR ANTIBODY AGAINST WESTERN EQUINE  
ENCEPHALITIS VIRUS

	Ordinary Comple- ment Fixation	Mouse Neutral- ization	CH50* Comple- ment Fixation
Normal rabbit serum . . .	..	—	..
Positive human serum . . .	+	+	+
Acute phase serum † . . .	—	—	—
Convalescent serum . . .	+(1:256)	—	—

\* Complement fixation employing the 50 per cent hemolytic unit method.

† Acute phase and convalescent sera also gave negative tests for antibody against the virus of St. Louis encephalitis using the CH50 complement fixation test.

terminal episode suggests a cerebral rather than a pulmonary vascular accident.

DR. ALEXANDER: That is a very interesting suggestion. How long did the terminal episode last, Dr. Knowlton.

DR. NORMAN KNOWLTON: About fifteen minutes.

DR. WOOD: I would agree with Dr. Mendeloff. I have seen patients recovering from poliomyelitis, for example, exhibit exactly the same picture.

DR. ALEXANDER: In summary then, it seems to be the general consensus that this patient had encephalitis from which she was recovering at the time she had a terminal vascular accident. Dr. Hunter suggests underlying vascular disease as a cause of the entire clinical picture. The terminal event was probably due to either pulmonary embolus or a cerebral embolus.

*Clinical Diagnoses:* Encephalitis, idiopathic, subsiding; multiple thrombophlebitis; pulmonary or cerebral embolization.

#### PATHOLOGIC DISCUSSION

DR. RICHARD L. SWARM: On opening the thorax the pleural cavities were free of fluid. In the superior vena cava there was a thrombus 6 cm. in length and 0.5 cm. in diameter that did not fill the lumen of the vessel and was at no point adherent to the wall. In the right ventricle were two emboli: one a thrombus 4 cm. long and the other a thrombus 13 cm. long that was folded upon itself. Angular clefts typical of venous valvular markings were present on all these thrombi. The abdominal viscera contained no significant changes except in the uterus which although of normal size had a hemorrhagic endometrium and congested myometrium. No thrombi were identified in the pelvic veins nor could any be expressed from the veins of the legs. The principal branches of the right and left pulmonary arteries were occluded in their more proximal portions by loose thrombi. At the base of the lower lobe of the right lung there was a pyramidal, partially depigmented infarct that measured 4 cm. in its greatest dimension. The lumen of a branch of the right pulmonary artery above the infarct was completely occluded by a firmly adherent thrombus.

In the posterior 10 cm. of the superior sagittal sinus there was a thrombus (Fig. 1) which was continuous into the right transverse sinus. This



FIG. 1. Organized thrombus occluding the posterior portion of the superior sagittal sinus. The cross section is exposed by the incision at the lower edge of the dura.

thrombus was firmly adherent to the wall and occluded the sinus. The straight sinus contained a thrombus in its posterior portion, but anteriorly and in the vein of Galen there was no occlusion. The central veins of the cortex and two or three pial veins over each hemisphere contained brown-gray thrombi which extended as far inferiorly as the Sylvian sulcus. The veins of the parietal and frontal convexity were congested, but over the inferior surfaces and occipital lobes the vessels were not remarkable except for one small thrombosed vein in the right occipital lobe. No destruction of the brain parenchyma was obvious on external examination, and on section there were only a few small foci of yellowish discoloration in the cortex of the superior part of the convexities of the frontal and parietal lobes. The arteries were normal. There were no pressure grooves.

DR. DAVID E. SMITH: The most remarkable gross findings were the thrombi in various veins and dural sinuses and a depigmented infarct in the lung. The emboli in the pulmonary arteries were undoubtedly the immediate cause of death although their source was not too obvious. They were large and long thrombi with valvular grooves to indicate origin in the veins of an extremity. Considering the fact the veins of the upper part of the right side of the body were still occluded, the veins of the legs were the most likely source of this terminal embolization of the lungs, notwithstanding the fact that no positive evidence of thrombosis in those sites was obtained within the limits of our examination.

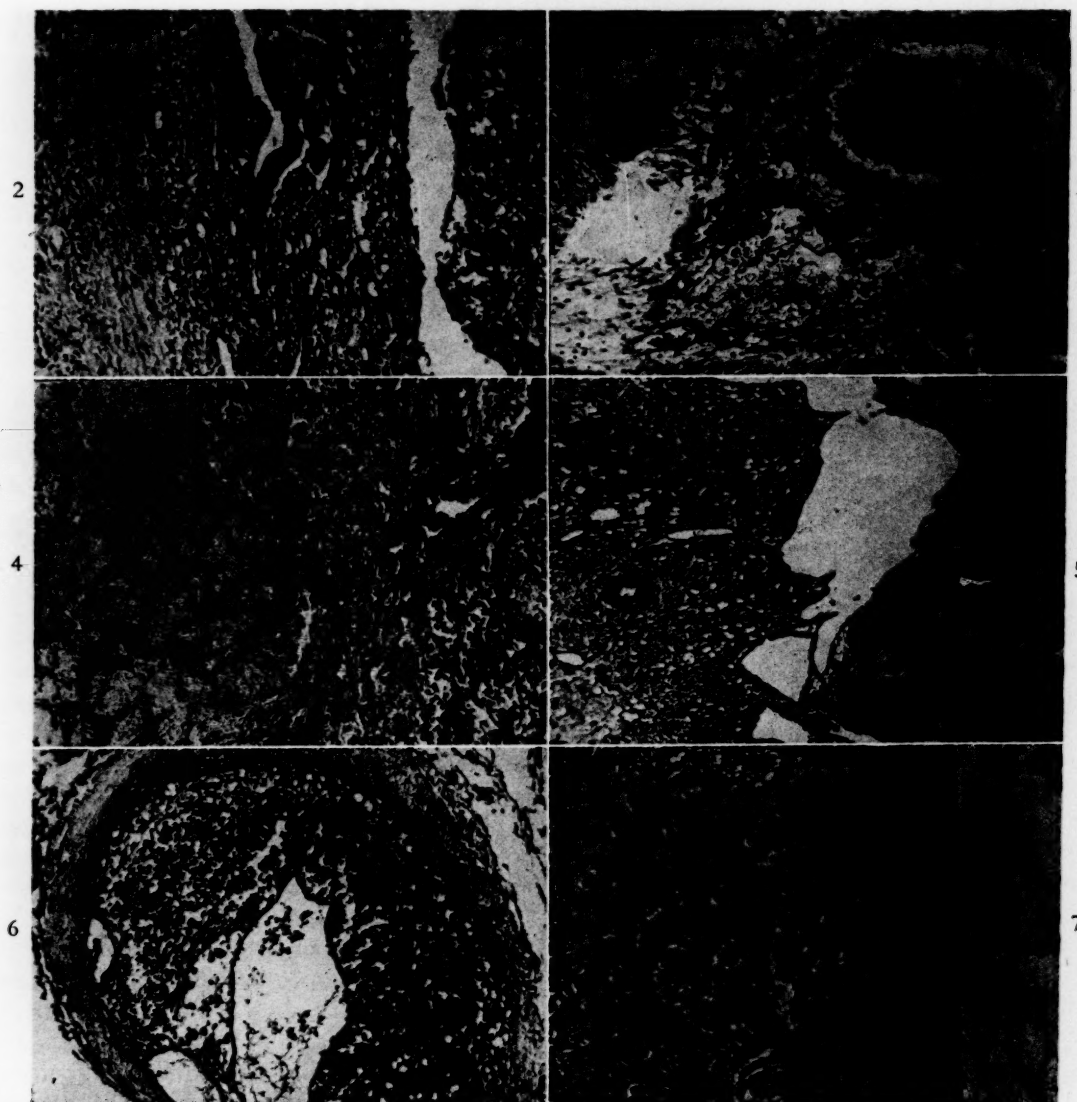


FIG. 2. Partially organized thrombus in the right axillary vein. The debris of red cells and fibrin on the right are the unorganized part that filled most of the vessel; estimated age: about three weeks.

FIG. 3. Completely organized and recanalized thrombus in a branch of the pulmonary artery near the infarct in Figure 4. The well developed vessel in the right upper corner suggests an age of several weeks longer than the thrombi in the axillary and jugular veins.

FIG. 4. A section of the depigmented and partially organized infarct in the lower lobe of the right lung. Depigmented infarcts of the lung are usually at least five weeks old.

FIG. 5. Organized and recanalized thrombus in the superior sagittal sinus. The well developed small vessels in the left side of the photograph suggest it is comparable in age to the thrombus and infarct in the lung.

FIG. 6. An organized thrombus in a pial vein over the cortex.

FIG. 7. A small focus of partially healed encephalomalacia in the upper cortex. These lesions are secondary to the venous occlusion and were the only ones found in the brain.

It remained for the microscopic investigation to determine whether there was encephalitis present at the time of death or whether there was any evidence that encephalitis had been present in the preceding nine weeks. It also became important to try to establish the relative ages of the thrombi in the various vessels.

Considering the latter problem first, Figure 2 illustrates a section of the thrombus in the right axillary vein. On the left side of the figure is the wall of the vessel. A relatively short distance from the wall, actually less than 2 mm. away, there is a mass of partially disintegrated fibrin and old red cells. Between these two structures is



a zone of fibroblastic proliferation and recanalization by sprouting vessels typical of organization of a thrombus. It is impossible to state exactly how old this lesion might have been, but it is compatible with the history of recognition of phlebothrombosis in the right arm three weeks before death. A section of the internal jugular vein showed an essentially similar zone of organization and a large central mass of unorganized thrombus. The amount of still unorganized thrombus and the thinness of the zone of organization were evidence that in these sites the process was still in an early stage.

The infarct and accompanying thrombus in the lower lobe of the right lung were older lesions. Figure 3 represents a section from the blood vessel at the apex of the infarct. A portion of the muscular wall lies in the upper left corner, and the entire lumen is filled with an organized tissue composed of fibroblasts. Within this typical organized thrombus, in the right upper portion of the field, there is a new vascular channel with a well developed muscular wall. The six weeks that are allowed by the history for the development of the lesion in the right thorax seem to be almost a minimum time for such a complete recanalization of a branch of the pulmonary artery. Figure 4 shows that the lower third of the pulmonary infarct was organized. The upper part was still unorganized and contained many laked blood cells between the dead alveolar walls. The minimum age of a depigmented infarct of the lung is about six weeks; so this lesion, too, is compatible with the period of time between the first negative roentgenogram and the second in which the lesion in the lower lobe of the right lung was first seen. The radiographic shadow was not actually due to the infarct but rather to considerable recently organized pleural exudate over the region of the infarct.

Sections of the sagittal sinus (Fig. 5) show a completely organized, recanalized thrombus that is remarkable for thick, well developed vessels of 100 to 200 microns in diameter which have a narrow zone of new muscle about them. Such a type of reorganization is certainly older than that in the axillary and jugular veins and seems comparable in age to the thrombus in the branch of the pulmonary artery. Figure 6 is of a section through one of the small pial veins. The vessel is occluded with loosely organized and recanalized tissue in which there are many macrophages filled with hemosiderin. In the

cortex (Fig. 7) the only type of histologic lesion that we were able to detect in multiple sections of this brain was a focal collapse of the second and third layers, loss of ganglion cells and proliferation of capillaries. This is typical of the type of reaction with occlusion of the pial veins and is not that of encephalitis.

The morphologic evidence is, therefore, well established for a thrombosis of the sagittal sinus of at least six weeks' duration. Careful examination of all parts of the brain showed no areas in which neurons had been destroyed, no focal calcification of small blood vessels and no persistent glial nodules. There are apparently no published descriptions of healed western equine encephalitis, but some papers that describe the changes following Japanese B encephalitis<sup>3</sup> as long as 11 weeks after the onset of the illness mention the prominent persistence of such lesions and something similar might be expected after equine encephalitis. Intracerebral inoculation in white mice of specimens of brain collected at the autopsy by Dr. Harford resulted in failure to isolate a causal agent. Of course this was a long interval after the acute illness, but it has been proved that St. Louis encephalitis virus can be isolated from the central nervous system of mice as long as five months after experimental inoculation.<sup>4</sup> This is then confirmatory, although perhaps not conclusive, evidence there was no virus present.

The source of the thrombus in the sagittal sinus is an interesting problem. There was no evidence of inflammation of the sinus; however, this patient had been delivered of a non-viable fetus some three weeks before the onset of her symptoms. Thrombosis of dural sinuses, particularly the superior sagittal sinus, is an uncommon but recognized complication of childbearing. Interestingly, the onset of symptoms is said to be most often in the third week after delivery and the thrombosis need not be septic. Martin,<sup>5</sup> writing in 1941 soon after Batson described the paravertebral venous anastomoses as a pathway for embolization from the pelvis to the dural sinuses, accepted that route as the

<sup>3</sup> ZIMMERMAN, H. M. The pathology of Japanese B encephalitis. *Am. J. Path.*, 22: 965, 1946.

<sup>4</sup> SLAVIN, H. G. Persistence of the virus of St. Louis encephalitis in the central nervous system of mice for over 5 months. *J. Bact.*, 46: 113, 1943.

<sup>5</sup> MARTIN, J. P. Thrombosis in the superior longitudinal sinus following childbirth. *Brit. M. J.*, 2: 537, 1941.

probable pathway of these thrombi in reaching the dural sinuses. Bland thrombosis of the pelvic veins in the last part of pregnancy, the trauma of delivery, propulsion of a thrombus into the veins of the spinal canal and from there into the cerebral veins is the postulated chain of events in such cases.

There was in this case, therefore, a thrombosis of the superior sagittal sinus that could certainly have accounted for this patient's cerebral symptoms and was compatible in its histologic appearance with the time of onset and duration of those symptoms. The appearance of symptoms in the third week after delivery was comparable with the usual course of postpartum thrombosis of a dural sinus. At about the same time a thrombus and infarct appeared in the lower lobe of the right lung. Although there were no changes in the uterus and pelvic veins at autopsy other than those expected in a uterus eleven weeks postpartum, the source of the lesions in the brain and lung was presumably in that region. Other findings indicated a pro-

gressive thrombosis of the veins of the upper part of the body during the last month of life and finally a fatal embolization of the pulmonary arteries by thrombi that had apparently developed concurrently in the legs. Although the clinical course of this case resembled that of encephalitis, there were no morphologic lesions to support that diagnosis; nor, after critical reinvestigation, were there any unimpeachable diagnostic clinical laboratory findings.

*Final Anatomic Diagnoses:* Postpartum involution of the uterus; organized thrombi in the superior sagittal and right transverse sinuses and the right internal jugular, right subclavian, right axillary and right brachial veins; focal, partially healed encephalomalacia of the cortex of the frontal and parietal lobes; loose thrombi in the superior vena cava, right ventricle and right and left pulmonary arteries.

*Acknowledgment:* The photographs were made by the Department of Illustration, Washington University School of Medicine, St. Louis, Mo.

# Special Feature

## The Western Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE FOURTH ANNUAL MEETING,  
SEATTLE, WASHINGTON, JANUARY 26 AND 27, 1951

**BLOOD MEDIA FOR THE CULTIVATION OF TUBERCLE BACILLI.** *Arthur W. Frisch,\* and M. Tarshis,* University of Oregon Medical School, Portland, Ore.

The experiments indicate that simple dehydrated agar media (Difco) incorporated with 25 per cent human bank blood are equal to or better than standard media for the cultivation of small numbers of tubercle bacilli, both from pure culture and directly from sputum specimens. The essential ingredient and limiting factor was shown to be human blood in a concentration of 5 per cent or more. The addition of egg yolk, glycerine or malachite green to the blood media rendered them inhibitory to the growth of tubercle bacilli.

The manner of preparation of the blood did not appear to be significant since similar results were obtained with oxalated, citrated and defibrinated specimens. It was also observed that bank blood as old as fifty days was as efficacious as freshly obtained blood. It is suggested that the blood media can be utilized for routine diagnostic purposes and for antibiotic sensitivity tests because of ease of preparation, minimal cost and ability to grow small inocula of tubercle bacilli.

**EVALUATION OF A HEMAGGLUTINATION TEST FOR THE DIAGNOSIS OF ACTIVE TUBERCULOSIS.** *William M. M. Kirby and James M. Burnell,* Department of Medicine, University of Washington School of Medicine, Seattle, Wash.

Hemagglutination tests (Middlebrook-Dubos) have been performed in 315 adult patients admitted to the infectious disease ward of the King County Hospital. Among 251 patients with non-tuberculous diseases, mostly acute infections, hemagglutinins were present in the sera of 123, and in 24 (10 per cent) the titers were 1:8 or higher. Thirty-one (57 per cent) of fifty-four patients with active tuberculosis had titers of 1:8 or above. Of thirty-nine patients with moderately or far advanced pulmonary tuber-

\* Asterisk indicates member of the Society; those not so indicated are by invitation.

culosis twenty-nine (75 per cent) reacted in a dilution of at least 1:8. On the other hand, negative tests were obtained with the sera of twelve patients with active tuberculosis. In patients with tuberculous meningitis, pericarditis and pleurisy with effusion, the test was negative or positive only in low titers, in most instances. The test was of little practical aid in diagnosis since positive sputum examinations were readily obtained in most of the patients with high hemagglutination titers, and false positive reactions occurred in 10 per cent of individuals with non-tuberculous conditions.

**IMMUNITY TO DIPHTHERIA AMONG ELDERLY ADULTS.** *Henry Brainerd,\* William Kiyasu, Mirra Scaparone and Louis O'Gara,* Department of Medicine, University of California School of Medicine, San Francisco, Calif.

Diphtheria has become a disease of adults in San Francisco, occurring predominantly in an age group previously considered highly immune. Active immunization of adults has been impractical because of frequent untoward reactions to toxoid.

One hundred sixty-four inmates of a home for the aged were studied in respect to Schick reaction, presence of circulating antitoxin and sensitivity to diphtheria toxoid (Moloney test). Of these 27.4 per cent proved to be Schick positive and 53.1 per cent proved to be sensitive to an intradermal injection of 1 to 20 dilution of purified toxoid. Thirty-three of forty-three Schick-positive individuals had less than  $\frac{1}{60}$  units of antitoxin per cc. of serum; eight had  $\frac{1}{60}$  unit but not  $\frac{1}{30}$  unit per cc.; and two had  $\frac{1}{30}$  or more unit per cc. The serum of two of ten Schick-negative individuals contained less than  $\frac{1}{30}$  unit of antitoxin per cc.

Twenty-three susceptible individuals received three intradermal injections of 0.1 cc. of purified diphtheria toxoid and thirteen individuals received 0.1 cc. of 1 to 10 dilution of the same toxoid at monthly intervals. Two local and one systemic reactions occurred in the Moloney-positive individuals.



The incidence of significant circulating antitoxin one month after two injections in twenty-one patients and the incidence of Schick negativity three months after three injections in all patients will be reported.

**ANTIBIOTIC ANTAGONISM: THE INTERFERENCE OF CHLORAMPHENICOL, AUREOMYCIN AND TERRAMYCIN WITH THE ACTION OF PENICILLIN IN EXPERIMENTAL INFECTIONS AND IN VITRO.** *E. Jawetz,\* J. B. Gunnison and R. S. Speck*, Division of Bacteriology, University of California, School of Medicine, San Francisco, Calif.

Antagonistic effects between the three "newer" antibiotics and penicillin have been demonstrated *in vitro* and in experimental infections of mice with both gram positive (hemolytic streptococcus) and gram negative (*Klebsiella pneumoniae*) organisms. The antagonism between penicillin and either chloramphenicol, aureomycin or terramycin extends over considerable ranges of concentrations of each drug, including concentrations commonly achieved in human body fluids with therapeutic doses. The phenomenon is limited by the degree of antimicrobial activity of each drug: Concentrations below the bacteriostatic level for a given microorganism as well as concentrations possessing marked bactericidal activity are without interfering effect.

Antibiotic antagonism is observed in experimental infections when the drugs are given at the same or different sites, in single or multiple doses. However, antagonism occurs only if chloramphenicol, aureomycin or terramycin are administered simultaneously with or prior to penicillin, not if penicillin is given first. Certain drugs which are synergistic with penicillin, e.g., streptomycin or bacitracin, can overcome antibiotic antagonism.

The experimental evidence indicates that the phenomenon is not one of mutual antagonism between the drugs concerned but rather an interference of chloramphenicol, aureomycin or terramycin with the early bactericidal and therapeutic effects of penicillin. The antagonistic drugs do not appear to interact physically or chemically so as to inactivate each other, but probably the "interfering" drugs modify the characteristics of the bacterial population so as to make it less susceptible to penicillin action.

**WHAT IS THE METABOLIC ANOMALY IN PERIODIC PARALYSIS?** *Frank H. Tyler,\** Department of

Medicine, University of Utah, College of Medicine, Salt Lake City, Utah.

Since the observation was made that hypokaliemia is associated with the attacks of weakness in certain patients having periodic paralysis, it has been widely assumed that the fundamental metabolic anomaly is one of potassium metabolism. We have observed a family in which thirty-three patients with clinically typical periodic paralysis are known and in whom the attacks have not been associated with hypokaliemia. The trait shows dominant inheritance. Microscopically, the muscle fibers show vacuolization.

In spite of the production of serum levels of 3.0 mEq. of potassium per L. by the simultaneous administration of insulin and glucose no change in muscular strength was observed. In addition, the failure of these patients to improve on oral potassium suggests that this periodic paralysis is different in its fundamental mechanism from other examples of the disorder. However, the poor correlation between the level of serum potassium and degree of paralysis in other cases reported in the literature as well as certain other findings raises the possibility that serum potassium depletion is not the primary mechanism in those cases as well.

**HISTOLOGIC STUDIES OF THE NORMAL AND DISEASED KIDNEY UTILIZING A NEW TECHNIC FOR DEMONSTRATION OF ACID MUCOPOLYSACCHARIDES AND OTHER ELEMENTS OF CONNECTIVE TISSUE.** *James F. Rinehart\* and Suleiman Abul-Haj*, Department of Pathology, University of California School of Medicine, San Francisco, Calif.

In disease, abnormalities of the mucopolysaccharide ground substance appear to be importantly involved particularly in rheumatic diseases and arteriosclerosis. In 1947 Hale described a method for histologic demonstration of the mucopolysaccharides based upon the affinity of the materials for colloidal iron. The method lacked selectivity and histologic clarity. We have modified the method in such a manner that the acid mucopolysaccharide can be clearly demonstrated and with appropriate counterstaining the other important element of the connective tissue including collagen, reticulum and basement membranes can be differentiated in a single preparation. The technic has proved particularly useful in the study of the kidney. This report is concerned with the de-

lineation of the histologic detail of the normal kidney and of the vascular and other nephritides.

The normal glomerulus shows a basement membrane which is evidently a product of the capillary endothelial cell. This is surfaced by epithelial cells which appear to elaborate a mucinous material that is probably an acid mucopolysaccharide. True collagen is not a constituent of the normal glomerulus and is rarely seen in the diseased structure. The obliterative changes occurring in glomerulonephritis involve proliferative reactions of the endothelium with new formation of the basement membrane substance. The glomerular lesions of diabetes are striking; they exhibit marked thickening of the basement membrane without noteworthy cellular proliferation. The "glomerulosclerosis" of diabetes does not involve "intercapillary" collagen but is evidently basically a disease of the basement membranes. In disseminated lupus there appears to be an excessive elaboration of the mucopolysaccharides on the surface of the capillary layer. The supporting tissue in the renal medulla is rich in mucopolysaccharide, which is removed if the section is treated with hyaluronidase prior to staining. In benign and malignant hypertension the lesions are, of course, dominantly vascular, and it is shown that the acid mucopolysaccharides play a very important role in the evolution of the vascular lesions.

**ALTERATIONS IN SERUM MUCOPROTEIN IN DISEASE.** *B. V. Jager\* and Margaret Nickerson,* Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

In the past eighteen months 500 estimations of serum mucoprotein have been made, using the method of Winzler et al. In many instances concurrent measurements with chemical methods were made of albumin, gamma globulin and fibrinogen, along with determinations of the sedimentation rate and packed red cell volume. Serial observations were made in a number of patients with infectious diseases and collagen disorders.

Findings were as follows: Alterations in serum mucoprotein have limited value in affording confirmatory evidence for the diagnosis of specific diseases. An increase in serum mucoprotein frequently constitutes a sensitive index of tissue injury. Serial estimations of mucoprotein in individuals with specific diseases may aid in estimation of progression or regression of

activity. Alterations in plasma fibrinogen in inflammatory diseases are more closely associated with alterations in serum mucoprotein than are alterations in gamma globulin and albumin.

**DEMONSTRATION OF THE LIVER AS THE MAJOR SOURCE OF PLASMA CHOLESTEROL.** *Meyer Friedman\* and Sanford O. Byers,* The Mount Zion Hospital, The Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

A series of experiments were devised in which both hypercholesteremic and hypocholesteremic states could be produced in rats. Following either of these two experimental procedures addition of cholesterol to plasma was found to be a function almost exclusively confined to the liver.

Hypercholesteremia produced by biliary obstruction in rats was found to occur despite concomitant surgical procedures such as castration, adrenalectomy, ligation of thoracic duct and total viscerectomy, indicating that the source of the excess plasma cholesterol occurring after biliary obstruction was not in any organ or tissue affected by the concomitant surgery. However, when either complete or subtotal hepatectomy was performed upon rats also subjected to biliary obstruction, hypocholesteremia did not develop.

Immediate reduction (70 per cent) of the plasma cholesterol of normal rats, experimentally achieved within twenty minutes, was followed by replacement of the lost plasma cholesterol within a period of twenty-four hours. This rapid return of the plasma cholesterol to normal levels was not seen in a second series of rats which were subjected to both experimental reduction of plasma cholesterol and subtotal hepatectomy. In these rats no more than a slight return of the plasma content of cholesterol toward normal occurred in a twenty-four-hour period (26 mg. per 100 cc. to 31 mg. per 100 cc.).

These results indicate that adequate and functioning hepatic tissue is necessary for either (1) excess discharge of cholesterol into plasma after biliary obstruction or (2) compensatory discharge of cholesterol into plasma after experimentally induced loss of cholesterol.

**EFFECT OF INSULIN ON GLUCOSE METABOLISM.**

*Douglas R. Drury,\* Arne N. Wick\* and Eaton M. MacKay,\** Scripps Metabolic Clinic, La Jolla, Calif., and Department of Physiology, University of Southern California, Los Angeles, Calif.



The metabolism of glucose has been studied with the aid of  $C^{14}$  labelled molecules. The extrahepatic tissues oxidize glucose to  $CO_2$  to a limited extent without the intermediation of insulin. Insulin increases greatly the oxidation of glucose by these tissues but this effect takes several hours to develop fully. During this time large amounts of glucose disappear from the blood stream. Much of the radioactive carbon is found in the blood and body fluids so that we must conclude that a large amount of intermediate compounds are formed as a result of insulin action. The chemical nature of these compounds is being studied.

**APPLICATION OF A MECHANICAL HEART APPARATUS TO EXPERIMENTAL CARDIAC SURGERY.** *Sanford E. Leeds,\* Irving Puziss and Bruce Friedman*, The Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, Calif.

A simple roller-type pump was employed to render bloodless the right heart of dogs. Blood was drained from both the cavae by means of a single cannula of special design. The caval flow was then shunted to the pulmonary circuit for oxygenation. It was observed that the pump had little effect on the elements of the blood. The plasma hemoglobin did not rise above 75.7 mg. per cent in any experiment even after four hours during which time 222.9 L. of blood passed through the pump. The determination of fecal urobilinogen after four, eight or twelve days further indicated that little red blood cell destruction occurred. The white blood cell count fell slightly or remained near the control level. The plasma  $CO_2$ , pH of the blood, hematocrit, plasma hemoglobin, blood sodium and potassium levels were little influenced by diverting the caval flow. The blood sugar became elevated, often becoming double the control value in thirty or sixty minutes. This has been observed with nembutal anesthesia without shunting of the blood. The arterial and venous oxygen saturation usually became very low within a short time after diverting the caval flow and remained low until the normal circulation was reestablished. In one experiment in which the animal survived after shunting the caval blood for sixty-eight minutes the arterial oxygen saturation remained at a level of 84.6 volumes per cent.

The blood flow through the pump was accurately determined and was found in fourteen experiments to be an average of 1.0 L. per

minute. The highest flow was 1.75 L. per minute. These values are 40 to 70 per cent of the normal caval flow.

Operations were successfully carried out on the right auricle and ventricle during the diversion of the caval flow. The auricle was open as long as eight minutes with survival of the animal. Large interauricular septal defects were successfully performed under direct vision with only slight loss of blood.

**DETECTION OF EARLY ATHEROSCLEROSIS BY A SIMPLE PROCEDURE FOR RECORDING PULSE CURVES.** *Norman A. David,\* George A. Weston and Elton L. McCawley*, Department of Pharmacology, University of Oregon Medical School, Portland, Ore.

Sphygmographs designed to record the arterial pulse wave have been useful to aid in the diagnosis of many cardiovascular diseases but the faults of cumbersome apparatus or the necessity of arterial puncture have prevented their practical application. We have developed a photoelectric sphygmograph which is simple to operate, causes no discomfort to the patient and is easily portable. The instrument operates by placing a beam of light on the arterial bed to be studied and converting red light reflected from erythrocytes into photoelectric current. As the pulse wave from the heart arrives at the area (tip of finger) illuminated, the distention of vessel walls produces a change in intensity of light and, in turn, a proportional change in photoelectric current. The resulting pulse wave, sphygmogram, is recorded on a portable direct-writing electrocardiograph. The electrical circuit of the instrument is so designed that records obtained are independent of the degree of oxygen saturation of hemoglobin and are not affected by volume changes or movements of the tissue being studied. The atherosclerotic pattern of the sphygmogram is recognized by its smaller size, flatter catacrotic and anacrotic limbs and absence of dicrotic notch. A second measure of arterial wall elasticity may be obtained by observing the velocity of propagation of the arterial pulse wave. The sphygmogram at a finger tip is recorded with an attenuated EKG superimposed so that the QRS appears as an artifact on the catacrotic limb of the just preceding pulse beat. The EKG paper can be read directly to determine the time required for the ventricle to close QRS until the pulse wave reaches the finger (systolic peak). This time and the distance from apex of heart to finger is



used to calculate velocity of propagation of the pulse wave. The mean elasticity (distensibility) of the arteries is derived from the formula

$$D = \frac{12.7}{(V_p)^2}$$

The elasticity was found to be significantly lower in the atherosclerotic group.

**PULMONARY VASCULAR BED MEASURED BY PERFUSION.** *Alvin J. Cox, Jr.,\* John S. Cheredes and Watson M. Lacy*, Department of Pathology, Stanford University School of Medicine, San Francisco, Calif.

The maximum capacity of the pulmonary vascular bed has been estimated by perfusion of human lungs postmortem through the pulmonary artery with kerosene. The rate of perfusion flow under standard conditions has been found to vary considerably in different individuals. Lungs from patients with chronic heart failure due to heart disease of various varieties exhibited restricted perfusibility as compared with controls. In four cases of chronic cor pulmonale resulting from pulmonary disease there was the most marked diminution in perfusibility of the lungs, which transmitted as little as one tenth of the maximum amount of fluid passed by control lungs. Although the bronchial arteries in some of the abnormal lungs were enlarged, the evidence afforded by these studies suggests that the major change in the circulatory system of such lungs is narrowing of the vascular bed of the pulmonary arterial system.

**CARDIOVASCULAR-RENAL ADJUSTMENTS IN COR PULMONALE.** *Ceylon S. Lewis, Jr., Arthur J. Samuels, Merrill C. Daines, Robert Carlisle, Filamon Ukradyha and Hans H. Hecht,\** Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

Eight patients suffering from chronic pulmonary disease with cardiac failure have been subjected to an analysis of their cardiovascular and renal responses and compared with normal individuals and subjects in congestive failure due to other causes. Cardiac output was determined by catheterization; peripheral, pulmonary and cardiac pressures were recorded and the usual indices calculated. A chromatographic-dye plasma volume (T 1824) was obtained simultaneously with total blood volume estimation using radioactive phosphorus. Renal clearance values were determined using paraaminohippurate and inulin.

The cardiac output and renal plasma flow in the "cardiac control group" (subjects with organic heart disease other than cor pulmonale)

was significantly lower than in normal subjects. Normal or high normal values were obtained for cardiac output in subjects suffering from cor pulmonale but renal plasma flow and glomerular filtration were depressed, and the filtration fraction was elevated (20 to 33 per cent, average 28 per cent) in approximately the same magnitude as in the cardiac control group. These findings are not compatible with the assumption that a lowered cardiac output is the major factor responsible for the altered renal hemodynamics in congestive heart failure.

**EFFECT OF INCREASED VENOUS RETURN UPON THE CARDIAC OUTPUT IN CONGESTIVE FAILURE.** *Herbert N. Hultgren and H. Schuyler Robertson*, Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

Patients with heart failure and elevated venous pressures will respond to firm compression of the upper abdomen by an increase in peripheral venous and right auricular pressure which can be sustained for the duration of the maneuver and which falls promptly when the compression is released. This maneuver produced increases in right auricular pressure of 50 to 240 mm. of saline in eight patients manifesting predominant right heart failure with an elevated resting venous pressure. Continued abdominal compression in this group sustained the elevations in right auricular pressure for five minutes. In six cases cardiac output determined by the Fick principle revealed a decrease in output of as much as 30 per cent below the resting value. The fall in output was associated with an increased AV difference, little change in oxygen consumption and was roughly related to the magnitude of the rise in right auricular pressure. In control subjects without heart failure no change in venous pressure or cardiac output occurred during abdominal compression. The results indicate that increased venous return to the failing heart may further decrease its output.

**SODIUM AND POTASSIUM RETENTION IN MYOCARDIAL INFARCTIONS.** *John J. Sampson,\* Kalmen Klinghoffer, Robert Kalmanson, Paul Toch and Meyer Friedman,\** Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, Calif.

In fifteen of twenty-one cases (71 per cent) of proven myocardial infarction the concentration and total excretion of sodium in the urine fell respectively to levels below 30 mEq./L. or 20

mEq./day and, in certain cases, to less than 1 mEq/L within three days after the infarction despite a sodium intake generally maintained between 2 to 3 gm. daily. Return to higher urinary sodium concentrations occurred in three to fourteen days in most cases. Decreased sodium excretion was greatest in patients with marked hypotension but occurred also in those not exhibiting a shock-like state or failure. Chloride excretion generally paralleled sodium excretion, as did potassium excretion in most cases, an inverse rate of urinary potassium excretion being manifest in only three patients. Changes in PCV and serum sodium concentration were of slight degree and did not correlate. Serum potassium concentrations showed no significant variations. Oliguria accompanied this salt retention in most of the fifteen cases and was severe in six. Four had an initial diuresis. There seemed to be no uniform correlation of glomerular filtration rate as determined by endogenous creatinine clearance with sodium retention.

Evaluation of adrenal cortical activity was attempted in thirteen patients, ten of whom had sodium retention. Eight of these showed an initial eosinopenia and four had significantly elevated uric acid-creatinine ratios. Ketosteroid determinations showed no consistent variations.

The results suggest that myocardial infarction generally produces a stress phenomenon with an hormonal, probably adrenal cortical, effect on renal tubules resulting in sodium retention.

#### LOW SODIUM SYNDROME AND HYPERPOTASSEMIA

INDUCED IN EDEMATOUS PATIENTS BY MECHANICAL REMOVAL OF BODY FLUID. *John J. Kelly, Jr. and Quentin B. Deming*, Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

It would seem reasonable to suppose that the removal of extracellular fluid by mechanical means (that is, by paracentesis or use of Southey-Leech tubes) would cause little or no disturbance in the electrolyte pattern, as the electrolytes should be drawn off in the concentrations that exist in extracellular fluid. Contrary to these expectations we have seen three patients with anasarca in whom the rapid removal of extracellular fluid by mechanical means was followed by the low sodium syndrome and hyperpotassemia. Diuretics and a reduced sodium intake had been employed in each of these patients.

Many factors are probably operative in producing this clinical picture but we believe that

the mechanism of action rests chiefly upon the following chain of events: (1) With the decrease in tissue pressure following the removal of fluid, the venous pressure and/or plasma volume decrease; a shock-like state follows. (2) As edema reaccumulates (in patients whose dietary intake of sodium but not of water is restricted) there is dilution of body sodium; this also may produce a shock-like state. (3) With (1) or (2) or both operative in any one patient, oliguria occurs and there is subsequent retention of potassium.

Case reports and supporting clinical observations will be presented.

ASSOCIATION OF RETROGRADE CONDUCTION WITH THE RECURRENT VARIETY OF PAROXYSMAL VENTRICULAR TACHYCARDIA. *David A. Rytand*,\* Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

In each of three recently observed patients with retrograde conduction to the auricles during paroxysms of ventricular tachycardia, the paroxysms were repetitive or recurrent rather than isolated. This unusual experience led to a search of the literature and our own files, with the following results: Retrograde conduction (with or without partial V-A block) was present in thirty-nine of seventy-five patients with recurrent paroxysmal ventricular tachycardia. This variety of paroxysmal tachycardia often is found without associated heart disease, as was true in twenty-six instances of the arrhythmia in which retrograde conduction appeared. On the other hand, retrograde conduction is extremely rare in isolated paroxysms of ventricular tachycardia; it was recorded in not more than five of nearly 100 such examples reviewed, and failed to appear in any of the eighteen subjects in whom a paroxysm was provoked by anesthesia, drugs or the intracardiac catheter. (The bidirectional arrhythmia which follows the use of digitalis glycosides was not included in this study, nor was paroxysmal ventricular tachycardia which complicated auricular arrhythmias.) Retrograde conduction was not apparent in any of thirteen patients with the Wolff-Parkinson-White syndrome and alleged ventricular tachycardia.

It appears then that the occurrence of retrograde conduction indicates a less ominous prognosis than usual for the outcome of any given paroxysm of ventricular tachycardia. Furthermore, it seems quite likely that the mechanism of production of repetitive paroxys-



mal ventricular tachycardia with retrograde conduction may differ from that of the isolated paroxysm without it; this is purely speculative.

**STUDY OF UNIPOLAR LEFT BACK LEADS IN THE DIAGNOSIS OF POSTERIOR WALL MYOCARDIAL INFARCTION.** *Stephen R. Elek,\* Lawrence Herman and George C. Griffith,\** Department of Medicine, Division of Cardiology, University of Southern California School of Medicine, and Los Angeles County General Hospital, Los Angeles, Calif.

The diagnosis of old or recent posterior wall myocardial infarction is dependent largely on the findings in lead aVF. In the horizontal heart position usually found in left ventricular hypertrophy and strain the aVF lead may not face the posterior wall infarct so that the latter diagnosis may be missed. Indeed, in the majority of Myers horizontal hearts with necropsy proven posterior wall myocardial infarction, lead aVF was not diagnostic. In order to remedy this diagnostic defect we have utilized unipolar leads taken from the left back using as anatomic landmarks the spines of thoracic and lumbar vertebrae (2, 4, 6, 8, 10, 12 and second lumbar). The electrode was placed about 2 cm. to the left of the vertebral spines and termed the spinous (Sp.) position. The anterior mid-clavicular line was projected posteriorly and this was labelled the scapular (Sc.) position. Leads were also taken along the posterior axillary line on the level with sixth and twelfth thoracic and second lumbar vertebral spines.

Unipolar left back leads were studied in forty-five normal patients without heart disease in the various electrical heart positions in order to determine the transition level from cavity Q wave to septal q wave. This transition occurs at the highest vertebral level in horizontal hearts, namely, Sc. 2 and Sp. 4, although in five patients the Q wave was still found down to Sp. 10. In left ventricular hypertrophy and strain the septal q wave was first seen at positions Sc. 2-4 and varied from Sp. 2-10.

Thirty patients (nine recent and twenty-one old) with posterior wall myocardial infarction were studied. The criterion for diagnosis was that of Myers: a Q wave in aVF which is at least 25 per cent of the R wave and at least 0.03 seconds or more in duration. The significant observation found was the occurrence of a Q wave deeper in relationship to the R wave as the electrode is moved from a higher to a lower

vertebral level in either or both the spinous and scapular positions.

The diagnosis of posterior myocardial infarction in the conventional leads was made in every case with the left back leads indicating the reliability of these leads. In two problem cases the interpretation of the QRS complex in lead aVF was elucidated by the unipolar left back leads which demonstrated the presence in one and the absence in the other of posterior myocardial infarction.

Hitherto, the diagnosis of posterior myocardial infarction has been dependent almost entirely on the findings in lead aVF. Unipolar left back leads constitute a useful method for bringing the electrode "closer" to the sight of infarction. In addition, our data indicate that they furnish further information regarding the electrical position of the heart.

**EXPERIMENTAL EVALUATION OF DRUGS FOR CLINICAL TRIAL IN AURICULAR FIBRILLATION.**

*Elton L. McCawley and George A. Weston,* Department of Pharmacology, University of Oregon Medical School, Portland, Ore.

Recent studies suggest the inadequacy of Sir Thomas Lewis' thesis that quinidine's effectiveness in auricular fibrillation is due primarily to a prolongation of the refractory period of the myocardium. In the evaluation of drugs before clinical trial in auricular fibrillation additional information is needed. We found in the intact dog that stimulation of the vagus directly, or indirectly by digitalis, methacholine or acetylcholine provokes auricular fibrillation or conversion of flutter to fibrillation. Application of quinidine or diphenhydramine exerts a clear-cut anti-vagal action although these drugs, unlike atropine, do not reverse peripheral hypotension. Both quinidine and certain of the antihistaminics reduce the electrical excitability of myocardium, which can be demonstrated in animals in which a greater intensity of electrical stimulation is required to evoke fibrillation after administration of these drugs. Moreover, a broadening of the T wave of the electrocardiogram is observed in dogs after injection of quinidine or diphenhydramine which may be interpreted as decreasing the repolarization rate of the heart. In further support of the theory that ectopic foci play an important role in the genesis of auricular fibrillation are those experiments which induce fibrillation by producing areas of crush injury or irritation by the injection of aconitine in the auricle of experimental animals. Since fibrilla-



tion can similarly be produced in the isolated rabbit auricle, the vagus would not seem to be an obligatory factor in the causation of fibrillation. Our experiments indicate that the more important factor in the conversion of clinical auricular fibrillation is the elevation of the threshold of myocardial excitability when quinidine or diphenhydramine is used.

#### IMMUNOCHEMICAL STUDIES OF ARCTIC ANIMALS.

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A program of research on the immunologic responses and protein chemistry of animals under stress of Arctic conditions was started in the latter part of 1948 with the support of the Office of Naval Research.

Preliminary results indicate that the Arctic squirrel is a good experimental animal for these studies. They form relatively high precipitating and hemolytic antibodies following a short series of injections of various antigens and these titers persist well into the period of hibernation. Electrophoretic studies of sera from squirrels as well as man indicate that some seasonal changes may occur in the plasma proteins, particularly in the gamma components and occasional appearance of albumins of greater than normal mobilities.

#### DIPHENHYDRAMINE INTRAVENOUSLY IN THE CONTROL OF VOMITING. *R. J. Kulasavage, W. R. Warrington and T. J. Pasquesi,* Department of Medicine, University of Oregon Medical School, Portland, Ore.

The complexity of the activity of vomiting or retching, involving the muscular actions of the stomach, esophagus, diaphragm and abdominal wall, requires the function of the medullary vomiting center for its occurrence. Selective depression of this center would, therefore, be effective in reducing or eliminating vomiting induced by many conditions. The efficacy of dimenhydrinate (dramamine) in this respect is probably attributable to that part of its structure which is shared with diphenhydramine (benadryl), but its usefulness is limited by the necessity for oral administration. A drug available for injection would be preferable for those numerous instances in which ingestion is useless or undesirable. Diphenhydramine, in doses up to 300 mg., has been given intravenously with no worse ill effect than drowsiness and, in two instances, brief visual hallucinosis. Five patients received diphenhydramine intravenously in eleven doses ranging from 35 to 100 mg. either in an infusion of other fluid or as an injection

of the 1 per cent solution, in attempting to terminate or interrupt vomiting or retching. Two were postoperative after anesthesia with nitrous oxide and oxygen; one was in the terminal uremia of chronic glomerulonephritis; and two had severe pain with disease undiagnosed at the time. Within minutes after the administration vomiting and nausea were completely absent. The shortest interval before return of those symptoms was two hours but in several cases it exceeded one day. This limited experience indicates that further study of the depression of the vomiting center by diphenhydramine and related substances is justified and such studies are now being undertaken.

#### CINEMATIC FLUOROGRAPHY. *Robert F. Rushmer,\**

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This film illustrates the practical applications of the cinefluorographic technic including: (1) a permanent record of the fluoroscopic appearance of the cardiac silhouette, (2) the localization of mediastinal tumors, (3) angiocardiology in experimental animals and in one case of infantile coarctation of the aorta, (4) visualization of the lungs and lung markings, (5) mechanism of swallowing and the passage of barium in the gastrointestinal tract and (6) movements and action of joints.

#### PARTITION OF RADIOPHOSPHORUS ( $P^{32}$ ) IN PATIENTS WITH HODGKIN'S DISEASE AND LYMPHOSARCOMA BEFORE AND AFTER NITROGEN MUSTARD. *S. P. Masouredis, B. V. A. Low-Beer, H. R. Bierman,\* L. S. Cherney and M. B. Shimkin,\** Laboratory of Experimental Oncology, Department of Radiology, and Department of Surgery, University of California School of Medicine, San Francisco, Calif.

The partition of tracer doses of radiophosphorus (300 microcuries) in tumor tissue, non-tumor tissue, plasma and urine of patients with lymphosarcoma and Hodgkin's disease has been followed before and after nitrogen mustard. Activity in tumor tissue and control tissue was determined *in vivo* by the surface counting technic. A characteristic triphasic concentration-time curve was obtained in the tissues studied. There was an initial rapid rise of activity followed by a rapid decline with subsequent slow decrease of activity over a period of days. These changes in activity occurred during the first sixty minutes after intravenous administration of  $P^{32}$ . Biopsy data obtained during this interval have shown that about 70 per cent

of the activity determined by surface counting is intracellular.

Of thirteen patients studied by this technic three have shown marked differences in the rate of  $P^{32}$  incorporation by tumor and non-tumor tissue following the administration of nitrogen mustard. Associated with this decreased rate of tissue  $P^{32}$  incorporated was a greatly increased urinary excretion of  $P^{32}$ . These patients with the above alterations of  $P^{32}$  incorporation and urinary excretion all received a good clinical response to nitrogen mustard therapy. In the remaining patients studied, who failed to respond clinically to nitrogen mustard, the uptake curves in tumor and non-tumor tissue and the urinary excretion of  $P^{32}$  after nitrogen mustard were the same as during the pretreatment period. The plasma concentration of  $P^{32}$  before and after nitrogen mustard was essentially the same in all the patients studied.

**INFLUENCE OF GROWTH ON THE DYNAMIC EQUILIBRIUM OF PROTEINS IN SUBCELLULAR COMPONENTS OF LIVER.** *Norman D. Lee and Robert H. Williams,\** Department of Medicine, University of Washington School of Medicine, Seattle, Wash.

DL-cystine labeled with  $S^{35}$  was injected intraperitoneally into normal Sprague-Dawley rats and those being fed p-dimethylaminoazobenzene (butter yellow) for eight, sixteen and twenty-four weeks. Eight hours later the livers were removed and separated by differential centrifugation into the following fractions: nuclear, mitochondria, microsomes and residual protein. The specific activities (counts per minute per micromol sulfur) of the liver tissue and its aforementioned components were determined and the extent to which each fraction participated in the protein turnover was evaluated.

In the normal rat the various fractions participated in amino acid incorporation as follows: mitochondria (1.00), residual protein (1.06), nuclear fraction (1.41) and microsomes (1.43). The apparent relationship between the nuclear fraction and microsomes, and mitochondria and residual protein, was maintained for eight weeks; however, they showed opposite responses with respect to the extent of amino acid incorporation. After eight weeks the amino acid incorporation activities of the nuclear fraction appeared to become related to the residual protein and the mitochondria to the microsomes. Furthermore, this nuclear-residual protein fraction decreasingly continued to participate in

amino acid incorporation and reversed itself at sixteen weeks whereas the mitochondrial-microsome fraction increasingly continued to participate in amino acid incorporation.

The neoplastic transformation may be described as an irreversible reorientation of biochemical activity. Probably the most meaningful parameter of such activity is that of protein synthesis. Whether the reorientations which we have reported are specific for the genesis of malignant tissue cannot be decided on the basis of the data obtained; however, similar experiments on the effect of dietary protein variation show entirely different responses and relationships, thus supporting the argument of specificity. Similar investigations are being conducted with respect to the influences of growth hormone and testosterone on these relationships.

**RESULT OF SYMPATHETIC BLOCK ON EFFECTIVE BLOOD FLOW THROUGH CALF MUSCLE.** *Samuel I. Rapaport, Chester Hyman, Mortimer E. Morton and Albert Saul,* Department of Physiology, School of Medicine, University of Southern California and Radio Isotope Unit, Veterans Administration Hospital, Long Beach, Calif.

The total blood flow in the toe and the effective blood flow in calf muscle were compared before and after lumbar sympathetic block in patients with vasospastic and occlusive vascular disease. Blood flow through the toe was measured by venous occlusion plethysmography; effective blood flow in muscle was estimated by the method of Kety which determines by external counting the rate at which locally injected radioactive  $Na^+$  or  $I^-$  disappear. That the tissue clearance may be used to evaluate effective blood flow has been suggested by previous workers and was indicated in a series of experiments in our laboratory in which an increased blood flow through the toe induced by reflex heating was accompanied by an increased clearance from subcutaneous tissue at the base of the toe. In all cases sympathetic block resulted in an increase in blood flow through the toe. In contrast, simultaneous measurement of tissue clearance of muscle was unaltered or slightly decreased.

These data are not in agreement with the findings of Barcroft and others who have convincingly demonstrated by venous occlusion plethysmography an increased muscle blood flow following sympathetic interruption. This difference may be due to a diversion of blood to the widely dilated distal vessels of the skin which could reduce effective blood flow to



muscle in spite of local dilatation. Such a diversion is prevented by the technic of venous occlusion plethysmography of the proximal limb. This possibility is now under study.

**PARTICIPATION OF THE ADRENAL CORTEX AND MEDULLA IN EXPERIMENTAL RENAL HYPERTENSION.** *L. J. Rather,\** Department of Pathology, Stanford University School of Medicine, San Francisco, Calif.

In association with hypertension induced in male albino rats by the removal of one kidney and constriction of the other with a silk ligature, there was found to be an increase in the weight of the adrenals directly proportional to the degree of cardiac hypertrophy. Hypertension did not develop in salt-maintained adrenalectomized rats subjected to this renal operation. In the largest adrenals hyaline intracytoplasmic bodies were found, chiefly in the zona fasciculata. These occurred in cells with large nuclei and nucleoli indicative of cellular hyperactivity, varied from two to eight microns in diameter, were insoluble in fat solvents and recolorized leucofuchsin after preliminary treatment with periodic acid. There is evidence to indicate that these bodies occur in response to hypophyseal corticotrophic stimulation. Measurements of cortical/medullary volume ratios in the enlarged glands and in controls show a decrease in the value of the ratio with increase in weight of the adrenals. Calculations of the absolute amounts of the cortical and medullary tissue indicate that with a two- or threefold increase in total weight the medulla may increase in weight fivefold or more. Although the increase in total adrenal weight is largely due to cortical hypertrophy and possibly hyperplasia, the degree of medullary hypertrophy and hyperplasia is relatively greater. This evidence of medullary hyperactivity in experimental renal hypertension points toward an important and hitherto neglected role of this tissue. There is evidence to support the contention that the adrenal medulla is involved in human essential hypertension.

**EFFECTS OF ACTH AND OF CERTAIN STEROID HORMONES UPON FATTY ACID AND KETONE METABOLISM.** *Laurance W. Kinsell,\* Sheldon Margen, George D. Michaels, Lenore Boling, John Partridge, and Gerald Liebert,* Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Previous reports from this laboratory have shown that ACTH and certain steroid hormones exert a major effect upon fasting-induced hyper-

ketonemia and ketonuria. If these agents<sup>†</sup> are given in sufficient dosage, such fasting-induced hyperketonemia can be almost or completely obliterated. From these observations it was postulated that one or more adrenal steroids increased the rate of utilization of aceto-acetic and beta-hydroxybutyric acids, and/or changed the metabolic pathway of fat in such a manner as to prevent the formation of ketone bodies as mid-zone metabolites. To evaluate these mechanisms two experimental procedures were devised and standardized. The first consisted of the administration of sodium aceto-acetate intravenously under standard conditions to normal and abnormal subjects. The second consisted of the administration of sodium octonate intravenously, also under standard conditions, to normal and abnormal subjects. During and following the period of infusion of the sodium aceto-acetate blood and urine ketone levels were determined. During and following the period of infusion of the sodium octonate, blood and urine octonate and ketone levels were determined. These procedures were carried out prior to the institution of any treatment, and then were repeated during the administration of ACTH and of certain steroid hormones, including cortisone.

The data so far obtained indicate that ACTH and some steroid hormones cause little or no stimulation of the rate of ketolysis, and that in some individuals there is evidence of major stimulation of the rate of utilization of infused octonate.

It would therefore appear that a major effect of ACTH and of certain steroids is to increase the utilization of fatty acids without increasing the rate of formation of ketone bodies. Data will be presented which suggest that a portion of this effect is referable to stimulation of the rate of neoglucogenesis from fat.

**ACTH IN CIRRHOSIS OF THE LIVER.** *Harold Brown, B. V. Jager\* and F. H. Tyler,\** Department of Medicine, University of Utah College of Medicine and the VA Hospital, Salt Lake City, Utah.

Four patients with cirrhosis of the liver were treated with ACTH in doses of 70 to 150 mg. per day for ten- to fifteen-day periods and observations were made on clinical status; glomerular filtration using inulin and endogenous creatinine, renal plasma flow and para-aminohippurate Tm; liver functions and histology; plasma volumes; plasma levels of protein con-



stituents, albumin, globulin, gamma-globulin and mucoprotein; excretion of 17-ketosteroids; hematologic changes and excretion and serum levels of sodium, potassium chloride, inorganic phosphate and creatinine.

There was a marked increase in appetite which became apparent on the first day of treatment in all four patients. In two patients the liver biopsy section showed a lessening of the fat and inflammatory reaction. In two patients there was a significant rise in hemoglobin and hematocrit despite the large amounts of blood (about 1,000 ml.) drawn for studies. The protein changes were not striking although the patients tended to show a rise in albumin and a drop in gamma-globulin and mucoprotein values. The renal clearances were unaffected by the ACTH therapy in the moderate doses used. The results of the other studies were in accord with the usual effects of ACTH.

ACTH seems of some value in the treatment of cirrhosis of the liver and merits further trial. The main salutary effects were an increased appetite and hematopoiesis. There was no change in renal function and no deleterious effect on the liver could be demonstrated by ACTH therapy.

**ORAL CORTISONE.** *Ephraim P. Engleman,\* Marcus A. Krupp,\* Peter Kunkel, Joseph E. Welsh and Mr. H. Wrenn, Veterans Administration Hospital, San Francisco, Calif.*

During the past six months forty-six patients have been treated with oral cortisone, using both tablets and cortisone suspension in syrup. Each patient had a disease known to respond favorably to intramuscular cortisone and severe enough to warrant the use of this hormone. The effects of oral and intramuscular cortisone have been compared as follows: (1) The oral dose of cortisone is similar to the intramuscular dose in its physiologic as well as therapeutic effects. This is substantiated by observations on twelve patients in whom both routes of administration were compared. (2) The therapeutic effect of oral cortisone is more prompt, a particular advantage in the treatment of acute disease. (3) The duration of action of a dose of oral cortisone is shorter, permitting prompt termination of the effects of cortisone should dangerous reactions occur.

The clinical impressions concerning the speed of absorption and excretion of orally administered cortisone have been substantiated by

urinary recovery experiments according to the method of Porter and Silber.

It is concluded that the oral route is the method of choice for therapy with cortisone.

**EFFECT OF DESOXYCORTICOSTERONE GLUCOSIDE (DCG) UPON CEREBRAL METABOLISM IN MAN.** *Richard C. Bentinck, Gilbert S. Gordan,\* John E. Adams, Tillie B. Leake and Thomas J. Huff, Divisions of Medicine and Neurological Surgery and the Metabolic Research Laboratory of the University of California School of Medicine, and the Langley Porter Clinic, State Department of Mental Hygiene, San Francisco, Calif.*

The striking mental manifestations which often accompany steroid administration in man have stimulated the authors to quantitate certain aspects of these compounds on cerebral metabolism. In the course of this study we have previously reported that the intravenous administration of desoxycorticosterone glucoside (DCG) to human subjects results in the liberation of a reducing substance from the brain into the cerebral venous blood. Further *in vivo* studies to determine the nature of this reducing substance and its possible precursors have indicated that the material is non-fermentable and presumably galactose.

Serial biopsy specimens of human brain obtained during therapeutic prefrontal lobotomy in psychotic patients, taken immediately before and after the administration of DCG, show a significant decrease in the gray matter glycogen content and an increase in the white matter glycogen. In addition, the reducing substance content of the methanol-chloroform-soluble fraction of the ethanol-insoluble moiety derived from a white matter alkaline hydrolysate is diminished, suggesting that the bulk of the reducing substance is derived from cerebrosides. Further characterization of the compounds involved is in progress. These studies and other data, to be presented, indicate that the steroids exert specific effects upon human cerebral metabolism.

#### PAPERS READ BY TITLE

**URINARY EXCRETION OF EXOGENOUS URONIC ACIDS.** *H. C. Bergman\* and B. S. Whittingham, Research Laboratory, Primorganics, Inc., Los Angeles, Calif.*

There are numerous reports on endogenous glucuronide excretion after administration of phenolic and other chemicals. However, no

published data could be found on quantitative urinary output of ingested uronic acids.

Eight tests were conducted in two fasting normal males. Each person ingested 2 to 6 gm. of galacturonic acid or glucuronolactone after collecting a one-hour urine specimen. Urines were collected hourly for the next five to six hours. Uronic acids were estimated by the method of Hanson, Mills and Williams. Equivalent weights of galacturonic acid and glucuronolactone gave identical calibration curves.

In fasting control tests one individual excreted an average of 11.3 (10.1 to 12.1) mg. and the other 12.5 (12.2 to 12.8) mg. glucuronic acid per hour. Urine uronic acid increased about 60 to 65 per cent over the initial output in one to three hours after intake of galacturonic acid. Increased excretion persisted for five to six hours. Only 1 per cent of the administered galacturonic acid appeared during this time. On the other hand glucuronolactone produced a seven- to ninefold increase over the initial output in the first hour. This declined to the original value in approximately seven hours. During this time 10 to 15 per cent of the ingested glucuronolactone was recovered in the urine.

Apparently the body may utilize 85 per cent or more of the uronic acids studied assuming, of course, complete intestinal absorption.

**EFFECT OF HISTAMINE UPON THE LEUKOCYTE LUNG REMOVAL MECHANISM IN MAN.** *Howard R. Bierman,\* Keith H. Kelly, Edward J. Smith and Nicholas L. Petrakis.* Division of Medicine, University of California School of Medicine, San Francisco, Calif.

The immediate leukopenia following intravenous histamine administration is well known. This leukopenia has been thought to be due to pooling of leukocytes in the spleen, liver and splanchnic capillaries associated with the hypotension.

By sampling blood from the right and left ventricle or large artery, it was possible to determine the number of leukocytes entering and leaving the pulmonary circulation during and after the intravenous administration of 0.1 to 0.3 mg. of histamine phosphate (as base). The findings indicate that the leukopenia is due to the cells being removed from the circulation by the lungs. Furthermore the decrease occurs exclusively in the myeloid series, the agranulocytes exhibiting no significant alteration. The leukopenia is transient and the lungs then discharge the myeloid cells into the circulation. This ebb

and flow tide of white blood cells into and out of the circulation can occur rapidly and is influenced by respirations.

These findings support the original contention that the pulmonary circulation contains a potent mechanism for controlling the leukocyte level in the peripheral blood in man. Further implications will be discussed.

**DISTRIBUTION OF DIGITOXIN IN THE ANIMAL BODY AFTER ITS PARENTERAL ADMINISTRATION.** *René Bine, Jr., Meyer Friedman,\* and Sanford O. Byers.* Mount Zion Hospital, the Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

The distribution of digitoxin in various organs and tissues of the rat, rabbit and dog was studied after parenteral administration of the glycoside.

Digitoxin when given intravenously to the rat (1 mcg./gm. of body weight) was found to enter all organs and tissues assayed (liver, kidney, heart, brain, lung, spleen and muscle) except the brain. The hepatic content of digitoxin immediately after injection (6.3 mcg./gm.) was three times that of the heart (2.0 mcg./gm.), the latter organ having approximately the same amount of digitoxin as the lung and kidney. Digitoxin content of these organs gradually decreased following injection but the liver of the rat continued to have much more digitoxin than any other organ or tissue assayed. Approximately three hours after injection the brain for the first time was found to contain digitoxin. Ten hours after injection the liver was found to contain twenty times as much digitoxin (1.2 mcg./gm.) as the lung, the heart or skeletal muscle. At this time the brain was found to contain three times as much digitoxin as the heart. Sixteen hours after injection only the liver and brain were found to contain detectable amounts of digitoxin (i.e., quantities of 0.05 mcg. or above). At the end of twenty-four hours no tissue was found to contain significant amounts of digitoxin.

Similar distribution of digitoxin was found in the organs and tissues of the rabbit and dog except that the liver of either of these species did not seem to concentrate digitoxin as did that of the rat, although a considerable concentration of digitoxin was found to be present in the medullary area of the kidney of these two species.

**USE OF AUREOMYCIN IN THE TREATMENT OF CONGENITAL FIBROCYSTIC DISEASE.** *Henry B. Bruyn,* Division of Pediatrics, University of California Medical School, and the Infectious



Disease Laboratory of the San Francisco City and County Hospital, San Francisco, Calif.

The major problem in the treatment of children with fibrocystic disease of the lungs and pancreas has been to control the repeated pulmonary infections which remain the principal cause of death. Antibiotics have prolonged the lives of these children and recently aureomycin has been reported to have value in the treatment and prophylaxis of pulmonary infections. The present study involves the use of aureomycin, over a period ranging from two to eighteen months, in twenty-eight proved cases of fibrocystic disease. All children had the constant cough characteristic of the pulmonary infection associated with this disease.

All children were placed on a dosage of 125 mg. of aureomycin given twice a day. Of these twenty-eight children five required increasing amounts of drug at intervals throughout the course of the study when the cough reappeared or increased in frequency. Weight gain and appetite were improved during aureomycin therapy in most instances. In seven children in whom aureomycin therapy was instituted within four months of the onset of symptoms of this disease, the course approximates that of a normal child. Five children died during therapy, two of these deaths attributable to fibrocystic disease alone. Twenty-four of the twenty-eight children had good results, with either marked diminution or complete disappearance of the cough characteristic of this disease.

Only one child has not tolerated the drug and has required other therapy. Two rashes, due to aureomycin, have necessitated a change to another antibiotic. Blood levels of aureomycin ranged between 1 to 5 micrograms/cc. of serum taken four hours after the last dose of drug and determined over a period of from one to six months of therapy. Throat and rectal bacterial flora changed very little qualitatively, but seemed to diminish quantitatively over the course of the study. Sensitivity to aureomycin was determined on all species of bacteria found in the throat and rectum at varying intervals of therapy. Sensitive as well as relatively resistant strains were found irrespective of blood level or duration of therapy.

It is concluded that up to the present time daily aureomycin is most effective in the management of congenital fibrocystic disease.

EXPERIMENTAL PRODUCTION OF NODAL RHYTHMS IN HUMAN SUBJECTS. *Merrill C. Daines and*

*Hans H. Hecht,\** Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

The observations by Wilson (1915) that the atrioventricular node of the normal human heart is released from the effects of vagal stimulation before the sinus node has led to the experimental production of abnormal auricular rhythms in normal young adults.

Twenty-five subjects (age twenty-two to thirty-four) received 1 mg. neosynephrine hydrochloride by vein. The peripheral effects of this sympathomimetic compound outweigh its cardiac action and, therefore, an abrupt rise in peripheral resistance without cardiac acceleration occurs immediately upon the injection. This is followed promptly by vagal reflex suppression of sinus activity with pronounced bradycardia and is characterized by the appearance of abnormal, slow, supraventricular rhythms, often preceded or followed by periods of excessive PR prolongation and auricular standstill. Various types of "coronary sinus" and atrioventricular nodal rhythms occurred lasting up to two minutes in twenty-three of the twenty-five subjects. Shifting of the abnormal pacemaker within the node occurred seven times.

The chain of events can be blocked by dibenamine and by atropine and can be interrupted by amyl nitrite. The ventricular complexes of the nodal beats showed almost invariably some alteration in form, suggesting that vagal stimulation may influence impulse conduction over ventricular tissue. The technic is useful for a number of clinical and physiologic problems.

CLINICAL TRIAL OF DIPHENHYDRAMINE IN AURICULAR FIBRILLATION. *H. Lenox, H. Dick and Elton L. McCawley,* Department of Pharmacology, University of Oregon Medical School, Portland, Ore.

Laboratory studies show that diphenhydramine resembles quinidine in its ability to prolong the refractory period of the isolated auricle, to elevate the threshold of the myocardium to electrical stimulation, to exhibit an antivagal action, and to convert induced auricular fibrillation and flutter in dogs or rabbits to normal rhythm. A mild atropine-like action and a synergistic action with epinephrine also has been observed. Toxicity studies in dogs indicate no serious untoward cardiac effects. We have compared the antifibrillatory action of diphenhydramine with quinidine in twelve patients with



auricular fibrillation. Patients were selected only on the basis that in our clinical judgment therapy with quinidine sulfate would be indicated. Diphenhydramine was given intravenously with continuous recording of the EKG and of other pertinent findings. With diphenhydramine alone there were six conversions to normal sinus rhythm which could be maintained by oral diphenhydramine. Conversion failed in two cases after intravenous diphenhydramine (insufficient dosage?) but large oral doses of quinidine sulfate were effective. In the other four patients underlying cardiac disease was probably responsible in preventing both diphenhydramine and quinidine sulfate from converting the fibrillation. Side effects noted were transitory drowsiness, vertigo, haziness of vision and frontal headaches which did not necessitate stopping the drug. Some rise in both systolic and diastolic (10–20 mm. Hg) pressures was observed. In one patient transitory visual hallucinations were noted following intravenous diphenhydramine while another showed some memory loss for recent events while on an oral maintenance dose. Further studies on the clinical usefulness of intravenous diphenhydramine and related antihistaminics are in progress.

**HYPOTENSION IN THE RAT FOLLOWING LIMITATION OF POTASSIUM INTAKE.** *S. Charles Freed and Meyer Friedman,\** Mount Zion Hospital, The Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

There is considerable information available concerning the necessity of adequate intake of potassium for preservation of the anatomic integrity of both the heart and kidney. Data, however, concerning the possible functional aspects of this relationship are scanty. A group of normal young rats therefore were maintained upon a synthetic diet very low in potassium (0.1 mg. of K/gm. of dietary substance). Blood pressures and body weights were recorded weekly upon these rats for nine weeks. Blood pressure was obtained by means of the microphonic manometer of Friedman and Freed. At the end of the nine weeks the rats were sacrificed and the essential organs were examined grossly and microscopically. For control purposes, groups of rats maintained upon (1) Purina laboratory chow and (2) experimentally synthetic diet plus KCl in drinking water were studied in the same manner.

The rats deprived of adequate intake of K exhibited a steady decline in blood pressure and a retarded gain in body weight. At the end

of the nine-week period their average blood pressure had declined from an initial control value of 100 mm. of Hg (range: 92–116 mm. of Hg) to 74 mm. of Hg (range: 68–86 mm. of Hg). The control rats, on the other hand, exhibited no significant deviation from their control blood pressure levels. Examination of the heart and kidney of these hypotensive rats indicated no correlation between the presence of myocardial or renal injury and the observed hypotension.

**RENAL EXCRETION OF DIGITOXIN AS AN INDICATOR OF ADEQUATE AND EXCESSIVE DIGITALIZATION.** *Meyer Friedman,\* Rene Bine, Jr. and Sanford O. Byers,* The Mount Zion Hospital, The Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

The renal excretion of digitoxin was determined in fourteen chronic cardiac patients who had been and were continued in an adequate state of digitalization (as indicated by clinical and electrocardiographic criteria). The renal excretion of the same glycoside also was determined nine times in seven subjects at the time they exhibited signs and symptoms of digitoxin intoxication. Assay of digitoxin in urine samples was accomplished by previously described methods employing the embryonic duck heart as the indicator of digitoxin concentration.

The experimental results indicated that an adequate state of chronic digitalization was indicated by a daily excretion of digitoxin not less than 21 nor more than 56 micrograms per day (average: 41 micrograms per day). This particular value was found to be approximately the same as that found in normal young subjects theoretically digitalized. Intoxication with digitoxin on the other hand was indicated by a renal excretion of digitoxin varying from 72 to 132 micrograms per day (average: 95 micrograms per day).

The finding of a renal excretion rate of digitoxin indicative of (1) adequate digitalization and (2) overdigitalization will be discussed both for its theoretic and its practical implications.

**SIMULTANEOUS MEASUREMENT OF SEVERAL COMPONENTS OF PLASMA AND INTERSTITIAL FLUID.** **PRELIMINARY REPORT.** *W. W. Hurst, F. R. Schemm\* and J. A. Layne,\** Great Falls Clinic, Great Falls, Mont.

Thirteen patients serve as the basis for this study. All had gross edema of cardiac origin. One had renal insufficiency in the near terminal state. Tissue fluids were obtained free of blood in the manner described by Burch. Components

measured are: *Sodium* (twelve studies). Tissue fluid sodium was lower in ten of the instances than in the plasma. The average over-all difference was 3.0 mEq./L. (1 to 7 mEq./L.). In the two exceptions the tissue fluid excess was 2 and 5 mEq., respectively. *Chloride* (eleven studies). Tissue fluid chlorides were higher than the plasma chlorides in all instances. The average difference was 9.3 mEq./L. (4 to 14 mEq./L.). *Carbon dioxide combining power* (nine studies). Tissue fluid values were higher than plasma values in all instances. The average difference was 13.7 volumes per cent (1.9 to 23.2 volumes per cent). *Potassium* (two studies). The respective values were the same. *Protein* (twelve studies). The average plasma total protein was 6.2 gm. per cent (4.6 to 8.6 gm. per cent); average albumin was 3.70 gm. per cent (2.3 to 5.1 gm. per cent; average globulin was 2.47 gm. per cent (1.7 to 3.8 gm. per cent). Tissue fluid total protein averaged 0.63 gm. per cent (0.33 to 1.10 gm. per cent); average albumin was 0.48 gm. per cent (0.17 to 0.86 gm. per cent); average globulin was 0.15 gm. per cent (0.01 to 0.39 gm. per cent). The plasma A/G ratio for the group was 1.5 while for tissue fluid it was 3.2. *Specific gravity* (twelve studies). The average plasma value was 1.0265 (1.0216 to 1.0298). Average tissue fluid value was 1.0092 (1.0076 to 1.0144). *Urea* (seven studies). In six instances the tissue fluid urea was higher than the plasma urea. In the remaining instance the values were the same. The over-all average difference was 6.6 mg. per cent (0 to 14 mg. per cent). *Non-protein nitrogen* (eight studies). Tissue fluid levels were lower than plasma levels in six, and identical in two. The average over-all difference was 8.2 mg. per cent (0 to 16 mg. per cent). *Cholesterol* (seven studies). Tissue fluid values were all recorded as less than 25 mg. per cent. Average plasma values were 177 mg. per cent (136 to 230 mg. per cent). *Direct and total reacting bilirubins* (eight studies). Tissue fluid direct values averaged 0.03 mg. per cent (0 to 0.1 mg. per cent), while the total bilirubin values averaged 0.09 mg. per cent (0 to 0.20 mg. per cent). Direct plasma bilirubin averaged 0.3 mg. per cent (0.1 to 0.8 mg. per cent), and the total values averaged 0.65 mg. per cent (0.1 to 1.8 mg. per cent).

#### ARTHRITIC SYNDROME IN DASF GUINEA PIGS.

Hugo Krueger, Rosalind Wulzen, Darrell Davis and Alice B. Plympton, Oregon State College, Corvallis, Ore.

Guinea pigs on diets deficient in the antistiffness factor (DASF) develop an accumulation of

calcium disturbances having marked similarities to arthritis in man. Roentgenologic examination shows thickening of the ribs, calcification of many cartilages and unusual depositions of calcium in bone and cartilage areas as well as in the soft tissues. For example, in guinea pig No. 1170 there were fifty-eight countable isolated areas of unusual x-ray absorption in the soft tissues. These areas were sharply delineated but of irregular outline and varied in diameter from 1 to 4 mm. Many of the areas represented irregular concretions lying under the skin and for some there was definite evidence of erosion toward the exterior. The areas of calcium deposition vary from animal to animal but the regions of the foot pads, knees, scapulae and retro-occipital areas are frequently involved. The foot pads of DASF guinea pigs usually become swollen and red and the position of the animal and the type of muscular movements are indicative of pain and an attempt to protect the pads from external stimulation. Roentgenograms indicate diffuse calcium depositions around and between the digits. In DASF guinea pigs many of the bones are altered by thickening, thinning or the development of exostoses. Very often the thickenings or the exostoses involve an alteration of the contour of foramina. Thus frequently the shape of the foramen ovale of the sphenoid is altered and its area reduced. This suggests the possibility of nerve compression and subsequent interference with sensory and motor nerve function.

CARDIAC CATHETERIZATION STUDIES IN PATIENTS WITH TRANSPOSED PULMONARY VEINS. David C. Levinson, George C. Griffith,\* Richard S. Cosby and Willard J. Zinn, Department of Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

Diagnosis of transposition of pulmonary veins has been established in four patients by direct passage of the catheter into a pulmonary vein from either the superior vena cava or right atrium. Two of the patients were acyanotic and had partial transposition. The third patient had complete transposition, and an operation anastomosing the left pulmonary to the left auricular appendage was performed. The fourth patient was cyanotic, had partial transposition of the pulmonary veins and was diagnosed as tricuspid atresia.

Oxygen studies and pressure determinations in the various chambers and great vessels are described.



**SODIUM ADSORBENT CATION EXCHANGE RESIN IN THE TREATMENT OF NEPHROTIC EDEMA.**

*Richard W. Lippman,\** Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif.

Sodium adsorbent cation exchange resin has been used in the treatment of fourteen patients with nephrotic edema and ascites during more than one year. Of these, eleven responded to a dose varying from 32 to 64 gm. per day with diuresis and chloruresis. An approximately edema-free state was reached in two to four weeks and this could be maintained by continued, intermittent resin administration. Of the three patients who failed to respond to this treatment only one was considered to have received adequate dosage.

Since the resin used exchanges ammonium ion for cations in the intestinal contents, in proportion to their occurrence, certain complications can be anticipated and occur. The principal difficulties are acidosis, hypokalemia and iron-deficiency anemia. Most of these can be avoided by intermittent resin administration. Special care must be used in diabetic patients and those with renal incompetence since they are already subject to the development of acidosis. Children must be watched carefully for listlessness and behavior changes, since these may be early signs of acidosis, which may be confirmed by determination of the carbon dioxide combining power of the plasma.

With careful attention the resin can be used successfully in the rehabilitation of patients who have been totally incapacitated by anasarca and ascites. No effect has been observed upon the course or progress of the underlying renal disease.

**ADRENALIN TEST IN HYPERSPLENISM.** *Arthur A. Marlow,\* and Robert A. Kallsen,* The Scripps Metabolic Clinic, La Jolla, Calif.

The hypotheses of "hormonal inhibition" and "splenic sequestration" have been used to explain the etiology of the cytopenic syndromes which are called "hypersplenism." The response of circulating blood cells to adrenalin has been described as being of diagnostic value in hypersplenism and has been reported by numerous investigators as a part of their work-up of cases of hypersplenism. We have found no attempts in the literature to correlate the responses to adrenalin in hypersplenism with changes which might be expected to occur normally or in the absence of the spleen.

The circulating leukocyte and erythrocyte changes after adrenalin in cases of hypersplenism were compared with those found in normal and splenectomized individuals. The initial leukocyte counts were lowest in hypersplenism and highest in splenectomized patients but the net gain in leukocytes was of the same magnitude in all three groups. Granulocyte and thrombocyte responses followed a pattern similar to the total leukocyte change. Erythrocyte changes in some instances of hemolytic anemia showed a greater net gain than that found in normal or splenectomized patients.

**EFFECT OF ACTH ON ADRENAL STEROID OUTPUT AS DEMONSTRATED BY RENAL VEIN CATHETERIZATION.** *Don H. Nelson and Hans H. Hecht,\** Department of Biochemistry, College of Medicine, University of Utah, Salt Lake City, Utah.

Greater levels of adrenal steroids have been observed in renal blood than in peripheral arterial or venous blood. This is presumably due to the adrenal vein opening into the renal vein.

The renal vein of normal humans has been catheterized and levels of adrenal steroids in renal blood measured before and after ACTH administration. By use of the technic it has been possible to demonstrate an increase in adrenal steroid blood levels following ACTH with return of these levels to normal.

**PURIFICATION AND PROPERTIES OF THE PHYTOHEMAGGLUTININ OF PHASEOLUS VULGARIS.** *Demetrios A. Rigas, Jonah G. Li\* and Edwin E. Osgood,\** Department of Medicine, Division of Experimental Medicine, University of Oregon Medical School, Portland, Ore.

The phytohemagglutinin of red beans (*Phaseolus vulgaris*) was recently isolated in pure form. The method of isolation consists of the following steps: (1) Extract the ground beans overnight with 1 per cent saline; (2) precipitate inert material by ethanol at final concentration of 30 per cent, pH 5.7, temperature  $-2^{\circ}\text{C}$ .; (3) precipitate the phytohemagglutinin from supernatant by ethanol at final concentration of 75 per cent and 1 per cent ethylether; (4) repeat this fractionation twice more; (5) dissolve the last precipitate in phosphate buffer, pH 8.0; (6) precipitate the inert material by 40 per cent saturation with ammonium sulfate; (7) dialyze the supernatant and lyophilize it and (8) repeat the ammonium sulfate fractionation. The yield is approximately 8 gm. per kg. of beans. The



purified phytohemagglutinin is heat labile, water soluble, of high molecular weight, giving positive protein and polysaccharide reactions and containing 4.3 per cent N. It is electrophoretically homogenous over a wide pH range, possessing a slow mobility and an isoelectric point around 5.6. It is therefore concluded that it is a mucopolysaccharide.

It is a powerful agglutinin for erythrocytes and its use in separating leukocytes for culture or chemical studies gives excellent results. The optimum amount for maximum recovery of leukocytes is about 0.1 mg. per ml. of blood.

#### INSULIN TOLERANCE TESTS IN PATIENTS RECEIVING LARGE DOSES OF EXOGENOUS INSULIN.

*Gerald T. Perkoff and Frank H. Tyler,\** Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

In 1938 Fraser et al. reported that the hypoglycemia caused by the administration of small intravenous doses of crystalline insulin to patients with islet cell adenomas is not followed by the hyperglycemia which occurs in normal individuals, a phenomenon referred to as hypoglycemia unresponsiveness. Although such an intravenous insulin tolerance test has been used extensively in the study of certain other disorders, e.g., adrenal insufficiency, its validity as a diagnostic tool in islet cell adenoma has been questioned, primarily because of variable results obtained by certain authors who have administered the insulin subcutaneously and because continued excess secretion of insulin has been thought to induce a state of relative insulin resistance.

In an attempt to test the importance of the latter objection we have performed intravenous insulin tolerance tests in patients receiving insulin shock therapy for psychoses. Each patient had received excessive doses of insulin five times weekly for several weeks.

The results of the insulin tolerance tests in these patients came within the limits of normal. The blood sugar fell to hypoglycemic levels at thirty minutes and returned to control levels or above at one hour. Thus it would appear that their insulin sensitivity remained the same in spite of the repeated administration of large doses of insulin.

**NATURAL HISTORY AND COURSE OF MALIGNANT HYPERTENSION.** *Mary F. Schottstaedt and Maurice Sokolow,\** Department of Medicine, University of California Medical School, San Francisco, Calif.

As part of a long range study of the natural history of hypertension, a survey was made of all cases of malignant hypertension seen in the past ten years at the University of California Hospital. Papilledema in the presence of severe hypertension was accepted as the criterion for diagnosis. One hundred four cases were included; follow-up information was obtained in all. The average survival after the discovery of papilledema was thirteen months in patients with good renal function and four months in those with impaired renal function. In ten well documented cases renal impairment developed in an average of 4.4 months. Autopsies performed in thirty-one cases revealed the basic renal lesion to be nephrosclerosis in twelve, pyelonephritis in twelve and glomerulonephritis in seven. The impression that nephrosclerosis is the most likely lesion when good renal function is retained in the presence of hypertension and papilledema was amply verified.

The following table summarizes the course of the disease in our group:

	Total	Survival over 30 Months	Papilledema Reversed
No specific treatment . . . .	88	3	2
Sympathectomy . . . . .	7	2	6
Low sodium, rice diets . . . .	8	2	4
Nephrectomy . . . . .	1	1	1

Only patients in whom papilledema disappeared survived more than thirty months. With the exception of one patient with glomerulonephritis, none in whom papilledema disappeared died of renal insufficiency. This is in contrast to the usual course in untreated patients. Disappearance of papilledema implies a decrease in tempo of malignant hypertension and reversal to benign hypertension. Provided vascular damage is not too extensive, an increased survival rate may be expected. Early and vigorous treatment is essential in malignant hypertension (1) before renal function is impaired and (2) before irreparable damage to cerebral and cardiac vessels has occurred.

**CARDIAC RESERVE IN EXPERIMENTAL MYOCARDIAL INFARCTION.** *Arthur Selzer\* and Gerard W. Taylor,* Department of Medicine and the Surgical Research Laboratory, Stanford Uni-

versity School of Medicine, San Francisco, Calif.

In an attempt to approach the problem of shock in myocardial infarction the response of the heart to acute strain was studied before and after the production of experimental myocardial infarction in the dog. Forty-five observations were made on nine dogs in acute experiments during which continuous recordings of pressure were taken from both ventricles.

The stimulus, a thirty-second obstruction of the thoracic aorta, produced in the control experiments a systolic hypertension in the left ventricle with slight or no raise in the end diastolic pressure but no change in right ventricular pressures, and with return to normal or subnormal levels upon release of obstruction. During the first two hours after the ligation of a large coronary branch with ensuing infarction, aortic obstruction had a similar effect upon pressures, except of somewhat higher rise in end diastolic pressure which was still reversible. Such a normal response to strain was also demonstrated in animals with myocardial infarction in which pressure was brought down to shock levels by bleeding.

In contrast to peripheral shock (due inadequate filling of the heart), cardiogenic shock (due to inadequate emptying of the left ventricle) was produced in two animals by ligating two coronary branches. In these the systolic pressure fell and the end diastolic pressure rose in the left ventricle only, and aortic obstruction caused no change in systolic but further rise in end diastolic pressure in the left ventricle indicating loss of reserve of an "overstretched" heart (Starling).

RECOGNITION OF PULMONARY STENOSIS. *Sidney S. Sobin,\* J. Patrick Meehan, Walter S. Thompson and C. Richard Baker*, Department of Cardiovascular Research, Childrens Hospital, Los Angeles, Calif.

Diagnostic cardiac catheterization in congenital heart disease in patients in whom the diagnosis cannot be made by simple clinical means has shown an unusually high and totally unsuspected incidence of pulmonary stenosis, both alone and in combination with other congenital cardiac defects. From the catheterization, angiocardiographic and clinical data a number of clinically recognizable forms of pulmonary stenosis have become evident.

EFFECT OF INSULIN ON VOLUME OF DISTRIBUTION OF GLUCOSE. *Arne N. Wick,\* Douglas R. Drury\**

and *Eaton M. MacKay,\** Scripps Metabolic Clinic, La Jolla, Calif., and Department of Physiology, University of Southern California, Los Angeles, Calif.

The glucose space of eviscerated rabbits has been previously reported and shown to be approximately 26 per cent of the body weight. This value is similar to that of other substances which distribute in the extracellular compartment. One theory concerning the action of insulin is that it increases the volume of glucose distribution. We have investigated this possibility using glucose uniformly labeled with carbon-14. Known amounts of glucose were injected while the animal was under the influence of insulin. The results show that the volume of distribution of glucose was not increased by the insulin administration. The disappearance rate of glucose is greatly increased. The problem of distinction between rapid distribution and slow penetration will be discussed.

STUDIES ON THE METABOLISM OF PROGESTERONE.

*John G. Wiswell and Leo T. Samuels,\** Department of Biochemistry, College of Medicine, University of Utah, Salt Lake City, Utah.

In 1947 Hooker and Forbes, using a bioassay in mice, reported a level of 4 to 8 micrograms of progesterone per ml. of blood from a pregnant woman. By means of a chemical technic which gives greater than 90 per cent recovery of progesterone added to blood in quantities of 1 microgram or less per ml., we have been unable to detect such amounts of progesterone in the bloods of pregnant women. At least two possibilities exist to explain this discrepancy: either progesterone is metabolized too rapidly to reach a significant titer in the circulating blood, or some other compound which has progestational activity is secreted by the corpus luteum.

As a means of studying the first problem we injected a female dog intravenously with enough progesterone to saturate its circulating plasma. Analysis of blood samples taken at intervals after the injection revealed that the progesterone practically disappeared from the circulation in fifteen minutes. Further studies are being made by obtaining blood directly from the ovarian vein of dogs. Also being investigated is the reason for urinary pregnanediol accounting for less than half the amount of progesterone injected into a human.



EFFECTS OF CONTRAST MEDIA ON THE MYOCARDIUM. Willard J. Zinn, George C. Griffith,\* David C. Levinson and Varner Johns, University of Southern California School of Medicine, Los Angeles, Calif.

Six consecutive illustrative cases are presented with direct-writer electrocardiographic tracings taken continuously until stable rhythm developed following injection of 75 per cent neo-iopax. The tracings show immediate ischemic changes evidenced by T wave inversion and occasionally "injury shifts" by depression of S-T segments. Beginning about three minutes after the injection ectopic ventricular foci appear and bursts of ventricular tachycardia may recur for up to twenty-seven minutes after the injection in the small group presented here. Adequate amounts of quinidine prevented the appearance of these irritable foci in a patient previously demonstrated to have ventricular tachycardia following the injection of 75 per cent neo-iopax. The pattern of ECG alteration after retrograde aortography significantly differs from the above and indicated the cause of the irritability noted. Seriously dangerous arrhythmias are frequent enough following injection of contrast media that constant ECG check during the procedure and cardiac premedication are warranted.

USE OF ORAL QUINDINE AND PROCAINE AMIDE AS PREMEDITATIONS FOR CARDIAC CATHETERIZATION. Willard J. Zinn, Richard S. Cosby, David C. Levinson, Harold Miller, Sim Dimitroff and George C. Griffith,\* University of Southern California School of Medicine, Los Angeles, Calif.

Seventy-six patients studied for cardiac catheterization arrhythmias were divided into "adequately" and "inadequately" premedicated groups. The "adequately" treated patients received either procain amide or quinidine in oral doses of 10 mg. per kg. of body weight immediately preceding the catheterization and two hours before the procedure. The "inadequately" premedicated group included patients given no premedication and patients given 0.2 gm. quinidine at three- or four-hour intervals for four to eight doses prior to catheterization. Procedures were classified as difficult, moderate and non-difficult. "Blind" technics in correlation of data showed the "adequately" premedicated were significantly better protected against dangerous disturbances of rhythm (three or more short bursts of ventricular tachycardia) or any ventricular, nodal or auricular arrhythmia which persisted longer than five seconds.



## Case Reports

# Acute Renal Insufficiency in Man Manifesting the Arterial Necrosis Observed in Dogs Following Bilateral Nephrectomy\*

E. E. MUIRHEAD, M.D. and ARTHUR GROLLMAN, M.D.

*Dallas, Texas*

THE acute renal insufficiency of man designated "lower nephron nephrosis"<sup>1</sup> is attended by recovery in most cases when a conservative regimen of therapy is followed.<sup>2</sup> The examination at post mortem of the nine fatal cases in our series has demonstrated the existence of serious extrarenal complications—pulmonary thromboembolism, fat embolism, miliary tuberculosis—which contributed greatly, if not mainly, to the ultimate cause of death. In the present paper we wish to report an unusual complication associated with a fatal case of acute renal insufficiency in which there was a definite rise of blood pressure during the period of observation of the patient and visceral arterial and arteriolar necrosis at autopsy. This vascular necrosis is of fundamental interest since it resembles closely the arterial and arteriolar necrosis encountered in dogs following bilateral nephrectomy and other alterations of the kidneys<sup>3</sup> but the counterpart of which, in the human, has not been previously stressed.

### CASE REPORT

A thirty-two year old white male who had been hospitalized twice during the past three years for schizophrenia was transferred to the hospital in a state of profound shock from the city jail where for the previous four days he had refused to take food or water. On the day of admission he was reported to have drunk about 2 L. of water, following which he vomited and

gradually sank into a state of coma. On admission to the hospital he manifested evidence of profound peripheral circulatory failure and signs of extracellular salt deficit. He was confused and irrational. The lungs were clear to percussion and auscultation. Neurologic examination was negative. A spinal puncture revealed normal fluid with an initial pressure of 180 mm. H<sub>2</sub>O and a closing pressure of 165 mm.

On admission the patient was given 200 cc. of 2.5 per cent sodium chloride, 2,000 cc. of Ringer-lactate solution, and 200 cc. of 50 per cent dextrose by slow intravenous drip and, because of muscular rigidity, 4 gm. of calcium gluconate intravenously. This resulted in disappearance of the signs of peripheral vascular shock and muscular rigidity. On the following morning the blood pressure was 140/90 mm. Hg.

In Figure 1 is depicted the patient's course during his stay in the hospital. As noted in the figure the urinary output remained at approximately 100 ml. throughout this period; the urine had a specific gravity of 1.005; albumin 2+. The azotemia which was evidenced on the day following admission gradually rose from 150 mg. per cent to over 500 mg. per cent on the day of death. Examination of the urine showed only a trace of barbiturate; no bromide was detected in the blood. The carbon dioxide combining power of the blood gradually declined from a level of 35 milliequivalents per liter to 14 milliequivalents per liter. The plasma chlorides which were elevated on the day following admission gradually receded to almost normal levels. Clinically, the patient appeared

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to be moderately dehydrated throughout his stay in the hospital.

During the first six days of hospitalization the mental state of the patient improved; he was cooperative and manifested interest in his surroundings but appeared listless. His blood pressure remained at a level of 140/90 for one week but rose sharply to 205/105 during the last three days of life, dropping gradually during the final hours before death.

The patient was treated conservatively during his period of hospitalization by replacement of fluid and salt losses. After control of the initial peripheral shock he received 5 L. of 5 and 10 per cent glucose in distilled water. On the second day of hospitalization diarrhea developed which continued throughout his hospital stay; the stools were tarry. To compensate for the loss of salt and water from the bowel and for the insensible perspiration he received between 2 and 4 L. of fluid intravenously daily, half of which consisted of 5 per cent glucose in water and the other half of Hartman's solution.

Autopsy was performed promptly before onset of rigor mortis. Grossly, the serous cavities appeared normal as did also the heart (weight 360 gm.), liver, gallbladder, bile ducts, pancreas and adrenals. Examination of the lungs (combined weight 650 gm.) revealed the presence of a slight amount of mucopurulent material in the bronchioles and small bronchi and an infarct 4 cm. in its greatest diameter in the right lower lobe near which an arterial branch was occluded by a thrombus. The remainder of the lung parenchyma appeared normal.

The gastrointestinal tract appeared normal externally but on opening the stomach it was found to contain a cast of clotted blood. The mucosa was dark red and covered with numerous adherent blood clots 5 to 15 mm. in size which when removed revealed small areas of ulceration in the mucosa. Similar lesions were encountered in the first and second portions of the duodenum; these were more pronounced in the latter. The mucosa of the remainder of the small intestine was intact but dark red in color, very friable and peeled easily from the submucosa. Fresh hemorrhagic ulcerations were also noted in the transverse colon and first portion of the descending colon. The entire small and large intestine was filled with blood.

The surface of the brain was moist and revealed several punctate hemorrhages in the posterior

horns of the lateral ventricles. The vermis of the cerebellum was partially destroyed by hemorrhagic necrosis and there was an area of encephalomalacia 2 cm. in diameter in the right cerebellar hemisphere posteriorly.

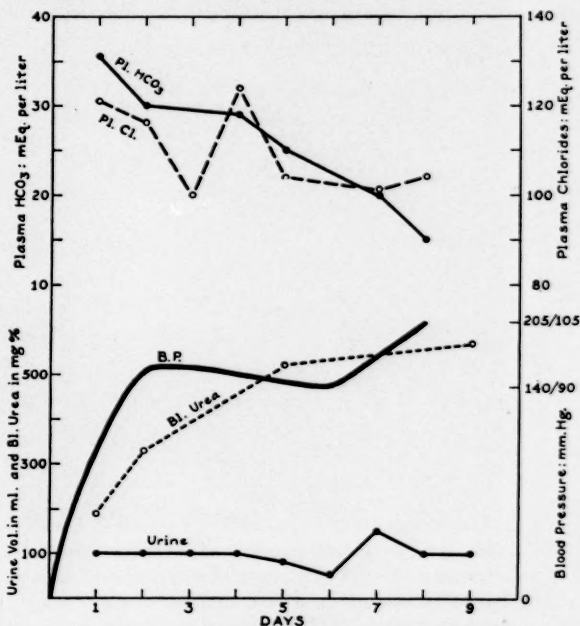


FIG. 1. The changes in plasma bicarbonate, plasma chloride, blood pressure, blood urea and urinary output in a patient observed following acute renal insufficiency and oliguria. All values are expressed in terms of mEq./L. except for the blood urea which is expressed in mg. per cent, the urinary output in ml. per day and the blood pressure which is plotted in terms of the mean pressure (diastolic plus one-third pulse pressure). The blood pressure was imperceptible on admission but rose to a level of 140/90 for the major period of observation and eventually reached a level of 205/105.

The kidneys were similar in appearance and weighed 150 and 160 gm., respectively. The capsules stripped easily revealing a smooth and pale surface. On cross section the edges everted; the medulla appeared hyperemic; the pelvis, ureters and urinary bladder were entirely normal. (Figs. 2 to 4.)

Microscopically, the heart, liver, spleen, pancreas and adrenals were entirely normal. Except for hypostatic edema, early bronchopneumonia and the area of pulmonary infarction previously described which revealed focal suppuration, the remainder of the lung structure was unaltered. The gastrointestinal tract revealed focal ischemic necrosis of the mucosa with neutrophilic infiltration throughout its length but this was more pronounced in the

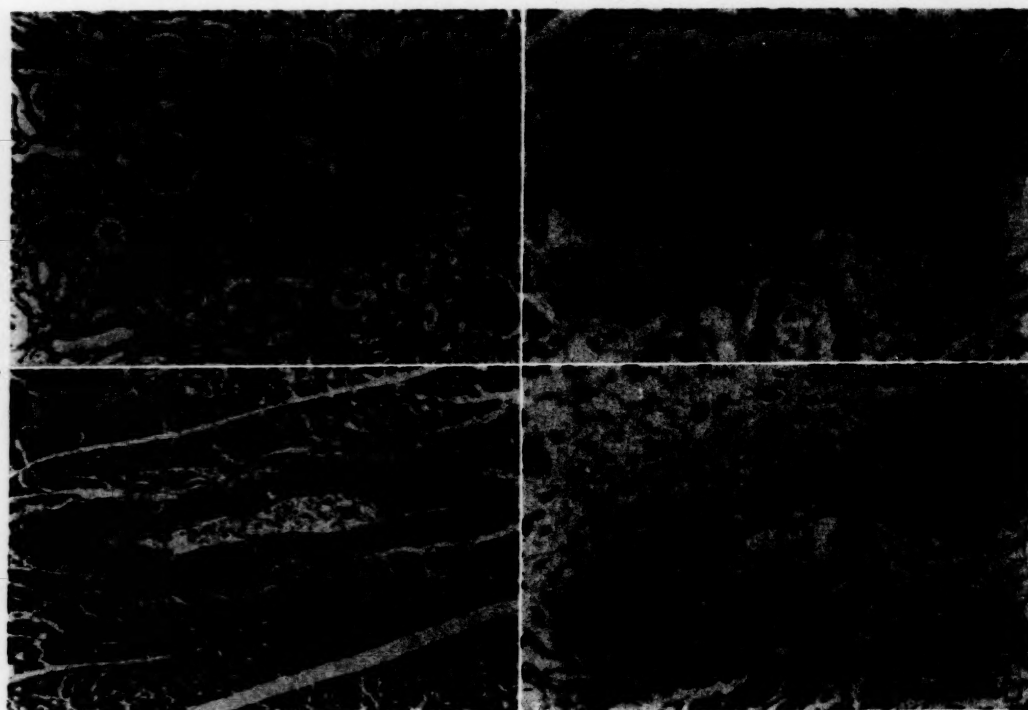


FIG. 2. A, photomicrograph of the kidney from the patient described in the text, depicting the tubular damage. Notice the normal glomeruli without arteriolar involvement. The main damage is in the distal segment in which there are many casts, desquamation, evidence of regeneration and focal inflammation. The proximal segments are partly dilated and reveal flattened epithelium, nuclear activity and a piling up of the epithelium;  $\times 120$ . B, a higher magnification of A showing the granular casts within altered distal segments of the tubules and a dilated proximal segment at the top of the figure showing irregularly flattened epithelium and granular debris in the lumen;  $\times 580$ . C, dog no. 7 died seven and one-half days following bilateral nephrectomy; mean blood pressure, 150 mm. Hg. A coronary arterial branch within the myocardium showing necrosis of the media, with extension of the smudged media into the adventitia; the endothelium remains intact;  $\times 500$ . D, an arterial branch in the submucosa of the stomach of our patient showing necrosis of the media with smudging and intact endothelium similar to that depicted in C,  $\times 580$ .

stomach and duodenum. Several sections revealed sloughing of the mucosa with ulceration. The submucosa was markedly edematous with scattered polymorphonuclear neutrophils and many necrotic arteries and arterioles. The media of these vessels had undergone necrosis with eosinophilic smudging with and without remaining pyknotic nuclear remnants. The endothelium of the vessels was intact but the smudged media extended often into the adventitia. Thromboses were not encountered. Rarely, a blood vessel within the muscularis revealed necrotic changes similar to those just described. The muscle fibers of the muscularis were swollen and at intervals were devoid of nuclei. This swelling of the sarcoplasm was in the form of oval hyaline masses with infiltration focally by polymorphonuclear neutrophils. The changes in the stomach and duodenum were most marked in areas where the vessels were affected. Similar altera-

tions of a lesser degree occurred also in the blood vessels and muscle of the colon.

Necrosis of the small arteries and arterioles was also evident in the vermis and right hemisphere of the cerebellum. In these there was also eosinophilic smudging with karyorrhexis and karyolysis of the media; however, unlike the vessels in the gastrointestinal tract those of the cerebellum revealed collapse of the media with occlusion of the lumina, the so-called thrombo-necrosis. Several vessels, however, revealed an intact endothelium. An occasional artery was occluded with an eosinophilic material resembling the necrotic media within which were strands of fibrin. Red cells were at times present within the necrotic media. The tissue surrounding the areas of vascular necrosis revealed encephalomalacia and small hemorrhages.

The kidneys revealed marked tubular damage, most marked in the distal convoluted seg-



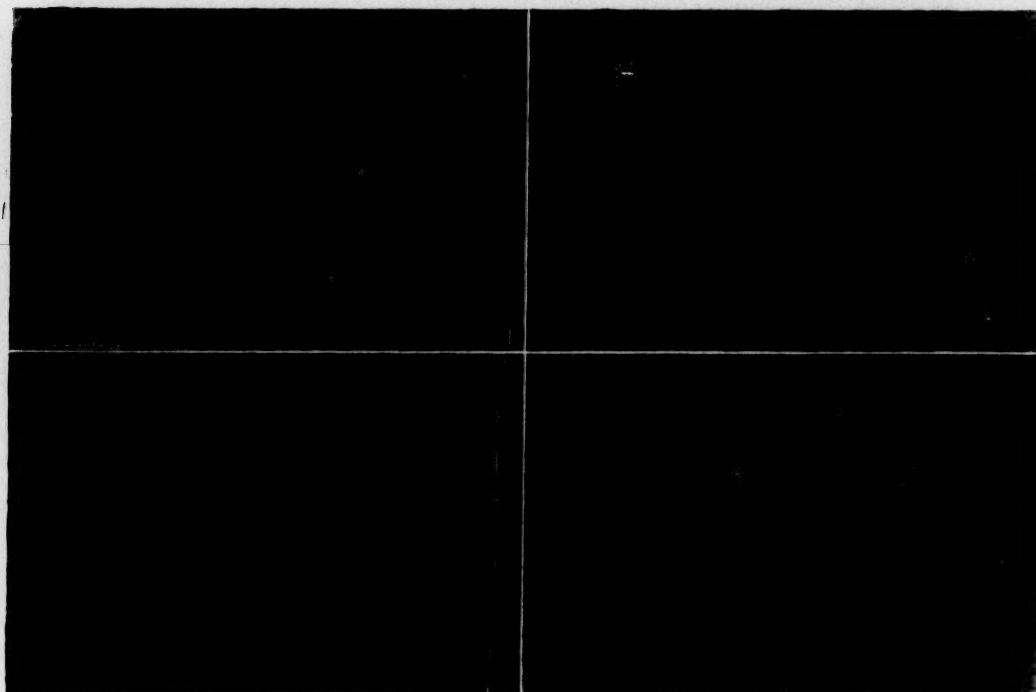


FIG. 3. A, dog no. 185, sacrificed seven days after bilateral nephrectomy; mean blood pressure, 170 mm. Hg. A small arterial branch in the submucosa of the stomach showing necrotic media and intact endothelium. Note the lumpy, granular character of the media and the early hyaline change. There is edema of the connective tissue surrounding this blood vessel;  $\times 580$ . B, a small arterial branch in the submucosa of the stomach of our patient showing changes similar to those depicted in A;  $\times 580$ . C, dog M1, died twelve days following bilateral nephrectomy; mean blood pressure, 180 mm. Hg. Small arterial branch in the submucosa of the stomach showing partial necrosis of the media; the endothelium remains intact;  $\times 580$ . D, small arterial branch from the cerebellum of our patient showing changes similar to C;  $\times 580$ .

ment, which contained many eosinophilic and granular casts surrounded at times by desquamated epithelium beyond which the tubular epithelium was of a flattened, recently regenerated type. The portions of the distal segments of the tubules which were devoid of casts were prominently dilated but there were foci of focal inflammation in areas where the distal segment had apparently disintegrated. A rare tubulovenous anastomosis was encountered. The collecting tubules, including the larger ducts of Bellini near the pelvis, also contained casts. The proximal convoluted segments showed evidence of damage but this was not as prominent as in the distal segments. Many of the proximal segments were dilated moderately and contained granular debris with a rare desquamated cell in the lumen. The epithelium was frequently irregularly flattened with an ill defined or apparently absent brush border. The epithelial cells were irregularly piled up in focal areas where multiple nuclei were evident. The glomeruli were intact and normal in appearance

as were also the arterioles and larger arteries. The capsule and pelvis also appeared normal.

#### COMMENTS

An elevation in blood pressure to approximately 140/90 mm. Hg is not uncommon during the course of so-called "lower nephron nephrosis."<sup>\*1, 2, 4-6</sup> In our own series of sixty patients an elevation to 160/100 mm. Hg or higher has been noted during the stage of renal failure in about 10 per cent of cases but this usually recedes to normal levels after the onset of diuresis. In two of our patients, however, a sustained elevation in blood pressure to about 180/100 mm. Hg was maintained following recovery, but

\* The term "lower nephron nephrosis" is used mainly because of its wide usage at present. It should be noted, as emphasized by others, that the proximal convolutions were likewise damaged in our patient and that, therefore, widespread rather than localized tubular damage had occurred.

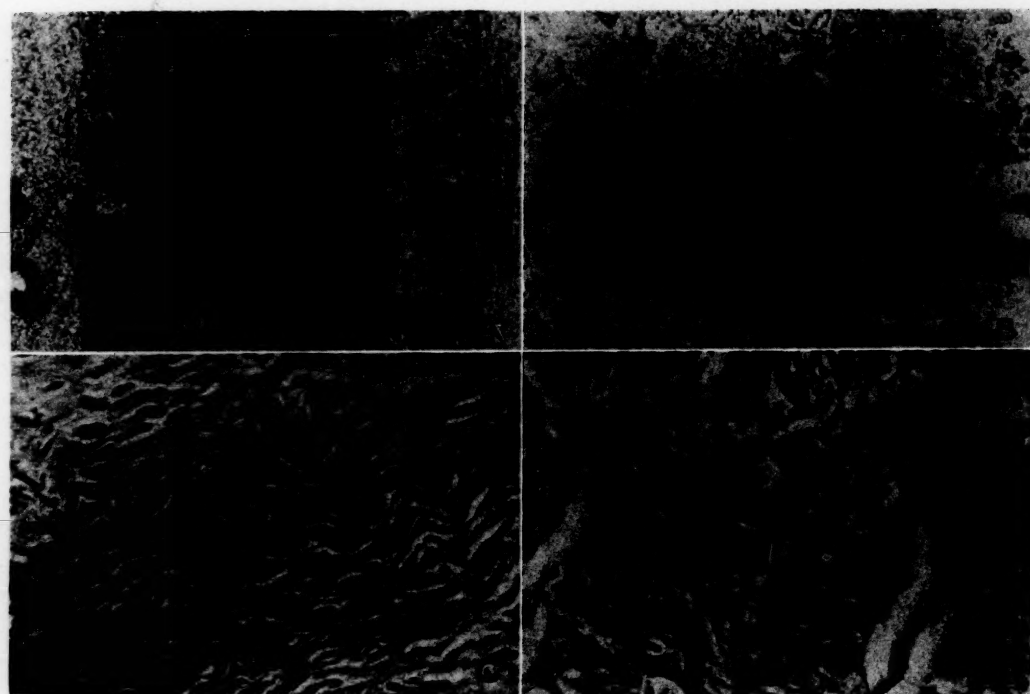


FIG. 4. A, dog no. 27, died six and one-half days after bilateral nephrectomy; mean blood pressure, 200 mm. Hg. Mucosa of the stomach showing necrosis with leukocytic infiltration and a necrotic vessel in the edematous submucosa;  $\times 100$ . B, mucosa of the stomach of our patient showing necrosis and sloughing. The submucosa is edematous and has foci of "fibrinoid" deposits. Compare with Figure 4A;  $\times 100$ . C, dog no. 75, died seven and one-third days after bilateral nephrectomy; mean blood pressure, 135 mm. Hg. Muscularis of small bowel showing hyaline swelling of smooth muscle fibers and focal absence of nuclei;  $\times 580$ . D, muscularis of duodenum from our patient with changes similar to those shown in C;  $\times 580$ .

receded to normal levels after a period of about six months. The case reported herein is unusual in that the patient developed a marked elevation in blood pressure during the course of the first week of his illness which was accompanied, as it is in the nephrectomized dog,<sup>3</sup> with visceral arterial and arteriolar necrosis. The latter condition apparently is uncommon in "lower nephron nephrosis" since it has not been mentioned by previous authors presenting large series of cases<sup>1,4-6</sup> except for Rather<sup>7</sup> who reported one case which at autopsy revealed necrosis of the small visceral arteries, photomicrographs of which depict arterial lesions similar to those observed in our patient.

Acute necrosis of the small arteries and arterioles has been observed experimentally as a result of a variety of procedures,<sup>3,8-15</sup> most of which involve damage or alterations in the kidneys which must be considered as factors in the genesis of this disorder. The

patient presented here demonstrates that a disturbance occurs in the human similar to that induced experimentally in the dog, particularly following bilateral nephrectomy. We believe that the rapidity with which the process is induced and the extent of the renal dysfunction (by damage or removal of renal tissue) accounts for its wide prevalence in the experimental animal. Only occasionally, as in our case in which a comparable disturbance with severe damage of both the proximal and distal segments of the tubules occurred, would a similar picture be produced in man.

#### SUMMARY

A case of "lower nephron nephrosis" following acute peripheral circulatory failure is described which was characterized by a rapid elevation in blood pressure to hypertensive levels and arterial and arteriolar necrosis of the blood vessels. The lesions

observed are similar to those seen in the bilaterally nephrectomized animal and in other experimental conditions in which acute renal insufficiency is induced. The identity of the process in the human and experimental animal is emphasized and attributed to the rapidity of the clinical course and to the extent of renal dysfunction which occurs in the two conditions.

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# Motor Neuritis after Tetanus Antitoxin with Involvement of the Muscles of Respiration\*

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THIS case is reported as an example of neuritis accompanied by weakness of the muscles of respiration occurring in a patient after an injection of tetanus antitoxin. Orthopnea was an outstanding symptom. Because he had no evidence of organic cardiac or pulmonary disease, the patient's dyspnea was suspected at first of being psychogenic. Recovery was slow; it began in six months and was practically complete in two years.

## CASE REPORT

S. L., a muscular, moderately obese white male, twenty-eight years old, 5 feet 10 inches tall, weighing 220 pounds, was spiked in the left ankle in a baseball game on August 3, 1947. The next day he was given an injection of tetanus antitoxin in the left deltoid region; there was no obvious sensitivity reaction. (An injection of tetanus antitoxin at the age of ten years had been followed by brief, severe urticaria.) On August 10th he began to have steady pain in the region of both shoulders. It was uninfluenced by respiration, position or motion of the shoulders. It increased so much in intensity that four hours later morphine was required for relief. For the next four days pain occurred periodically in the shoulders and extended to the region of the first thoracic spine. Numbness developed down both forearms and was pronounced in the right thumb. On August 14th he complained that his chest felt heavy and that he became dyspneic upon lying down. His physician referred him to the Hospital of the University of Pennsylvania.

Physical examination disclosed some tenderness over the right deltoid and biceps muscles and in the right thumb. Dr. A. M. Ornstein, who saw him in neurologic consultation on

August 18, 1947, noted weakness of the right deltoid and absence of reflexes in the arms; he found no sensory abnormalities at that time. He made a diagnosis of "post-tetanus antitoxin brachial neuritis."

During this first admission his pulse varied from 80 to 95, respiration from 18 to 24 and blood pressure from 120/90 to 145/100; temperature was normal. Hemoglobin, white blood count and ECG were normal. Plasma CO<sub>2</sub> content was 25 mM/L. (56 vols. per cent), serum calcium 11.2 mg. per cent and chlorides 97.8 mEq./L. X-ray of the cervical spine was negative. X-ray and fluoroscopy of the chest showed that the hemidiaphragms, especially the left, were high but disclosed no cardiac or pulmonary abnormalities.

He continued to have severe, periodic pain in the shoulders, arms, hands and upper dorsal region, and dyspnea when lying supine even when his head was elevated. He could sleep only in a sitting position. He noted that his sneezes and coughs were "weak." The cause of the patient's dyspnea was puzzling. Because his chest seemed to expand well and the diaphragm appeared to move, the dyspnea was thought at first to be psychogenic rather than due to involvement of his respiratory muscles. The patient was permitted to leave the hospital on August 29th.

When seen again, September 2, 1947, his pains had largely subsided but his right biceps muscle had atrophied markedly. Except for weakness of the right arm his only complaint was inability to breathe normally. He had made the following observations related to his breathing: Standing, he had no breathlessness. Sitting, he became breathless when talking, after eating a large meal or when his belt was too tight. He could blow his nose vigorously but he could not

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inspire strongly. He could not sneeze normally; when he sneezed he felt a weak "shock" in his chest. A few days before he had gone to a swimming pool; he noted upon walking into deeper water that when the water level reached his costal margin he became a little dyspneic and when it reached his neck he became so short of breath that he had to get out of the pool immediately.

We observed his breathing when he was in various positions. When he was standing and sitting, it seemed normal and his chest expansion appeared to be adequate. However, when he lay on his back, within a few seconds he began to make powerful abdominal movements in an attempt to breathe. He became cyanotic, apprehensive and in ten to fifteen seconds had to sit up. When he lay on the right or left side, he breathed fairly well at first but could not continue in this position for more than a minute or two. When he lay prone, he breathed with great difficulty; but if he supported himself on his elbows so that his chest and abdomen did not touch the examining table, he was able to breathe quite well.

Fluoroscopic study of the chest (patient in erect position) showed that both hemidiaphragms were very high. They moved much less than normally on forced inspiration (right 2 cm.; left 2.5 cm.). The lung fields seemed to be much more cloudy than normal unless he took a deep breath. Fluoroscopy was not performed with the patient supine.

These findings indicated weakness of the muscles of respiration. The following further observations (Table 1) supported this conclusion.

Measurement of the circumference of the chest at the levels of the axilla, nipples and costal margins during full expiration and again during full inspiration (either voluntary or "forced" by inhalation of 10.4 per cent CO<sub>2</sub>) showed practically no change in the girth of the chest (maximum, 3 mm.), despite the fact that he appeared to be expanding his chest.

He was placed, supine, in a Drinker respirator and remained comfortable for twenty minutes.

When he was sleeping in the high Fowler position, the head of the bed was lowered slowly. He awoke immediately with severe dyspnea.

His vital capacity was low when he was standing (2,440 ml.) and sitting (2,350 ml.). If he inspired fully in the sitting position and then lay supine, he could exhale 2,200 cc. by maximal effort. If, however, he performed both inspira-

tory and expiratory efforts in the supine position, his vital capacity was only 600 ml.

The patient found it difficult to inspire forcefully or rapidly but once he inflated his lungs he could exhale fairly rapidly. Standing he could raise a column of mercury 80 mm. by maximal

TABLE 1  
RESPIRATORY DATA IN PATIENT S. L.

	9-5-47	9-24-47	5-29-50	Calculated Normal
Vital capacity (ml.), standing....	2,400	2,200	3,930	4,300
Vital capacity (ml.), sitting....	2,350	2,050	3,800	4,300
Vital capacity (ml.), lying, right side.....	900	1,050	....	4,300
Vital capacity (ml.), lying, left side.....	1,000	1,000	....	4,300
Vital capacity (ml.), supine....	600	500	3,520	4,300
Chest expansion (cm.), voluntary	0.2	1.0	4.0	7.0
Chest expansion, 10% CO <sub>2</sub> .....	0.3	....	....	....
Min. vol. resp. (L./min.)				
Sitting.....	13 (24)*	....	9.3 (13)	7.0
37.5° angle.....	17 (34)	....	....	....
Supine.....	2 est.	....	10.6 (18)	8-10
Supine, Drinker.....	....	8 (18)	....	....
Sitting, 10% CO <sub>2</sub> .....	40 (32)	....	....	76 (35)
Standing, max. vol. (MBC)....	98	86	145	160
Breathholding (sec.)				
Sitting, air.....	26"	....	50"	60"
Sitting, O <sub>2</sub> .....	68"	....	....	120"

\* Figures in parentheses refer to frequency of breathing.

expiratory effort (normal, 107), but could lower it only 36 mm. by maximal inspiratory effort (normal, 86).

When he sat quietly the patient's minute volume of breathing was greater than normal. The amount that he could increase this by maximal voluntary effort (maximal breathing capacity) was less than the predicted normal value.

As a result of the observations recorded above it was concluded that: (1) There was marked weakness of all the muscles of respiration, which was not enough to interfere with normal resting requirements in the sitting or standing position but was sufficient to cause respiratory disability when breathing was hampered by restriction of diaphragmatic movements (lying down, ingestion of a large meal, tightening of his belt); or by restriction of thoracic movements (standing in water up to his neck); or when he was forced to increase his breathing (voluntary hyperventilation, inhalation of 10.4 per cent CO<sub>2</sub> or severe exercise). (2) The weakness involved muscles of inspiration more than those of expiration. (3) The patient's dyspnea was due to physical disease; it was not psychogenic.



The patient was seen as an out patient on September 25 and October 29, 1947, and on January 13, 1948; there was little improvement in his respiratory power. He did not return again until May 29, 1950. He informed us that his breathing and weakness of his right arm had improved slowly and gradually until by the summer of 1949 he had felt almost normal. In the spring of 1950 he had reduced his weight 40 pounds by dieting. He now believed that he was physically fit and intended to return to active participation in athletics. The respiratory studies made at this time (Table 1) showed a return of the figures toward normal.

#### COMMENTS

It seems probable that this patient's muscular weakness was caused by neuritis following the injection of tetanus antitoxin of the type reported by Wilson and Hadden.<sup>1</sup> We do not know of another instance in which weakness of the respiratory muscles has been reported in this condition. The paralysis of the thoracic respiratory muscles appeared to be complete, that of the diaphragm appeared to be partial. This pattern is compatible with involvement of spinal roots from the fourth cervical to the eighth and ninth thoracic segments.

We administered neostigmine methyl sulfate (1 mg. intramuscularly) to this patient early in the course of this disease (August 12, 1947) because of the beneficial effects reported by Blattner, Goodfriend and Webb<sup>2</sup> in a patient with infectious neuronitis which occurred following measles. We could not detect any improvement in our patient by objective tests; there was no change in the strength of the hand muscles (dynamometer test) or of the respiratory muscles (measurement of vital capacity in different positions).

Most of the reported cases of neuritis after tetanus antitoxin seem to have recovered more rapidly than our patient did. He began to improve only after six months and did not feel normal for two years. Nevertheless, his recovery seems complete or nearly so. He was given large doses of vitamin B complex but we have no evidence that this had an important effect on the course of the disease. The reduction in weight, which he instituted somewhat tardily, seems to have reduced his respiratory symptoms, probably by lessening the work of the diaphragm.

Some explanation should be offered for the severe dyspnea that developed in this patient

within ten to fifteen seconds after he lay down. If it were due entirely to abnormal activity of the Hering-Breuer vagal reflexes initiated by elevation of the diaphragm and compression of lung tissue, the dyspnea should have been abrupt in onset. Actually it increased progressively over ten to fifteen seconds, and the patient could tolerate the horizontal position for two minutes when O<sub>2</sub> was substituted for air without his knowledge. This latter observation indicated that arterial anoxemia was an additional factor. Arterial blood samples were not analyzed for O<sub>2</sub> but arterial O<sub>2</sub> saturation (measured by the oximeter) decreased 7 per cent within fifteen seconds after our patient, breathing air, lay supine. The patient had a large abdomen. It is likely that in the supine position the weight of the abdominal contents prevented the weakened diaphragm from producing any effective ventilation; since the thoracic muscles were known to be paralyzed, assumption of the supine or prone position thus stopped all pulmonary ventilation and produced a state equivalent to breath holding. However, a healthy person can hold his breath longer than fifteen seconds without any detectable decrease in the oximeter reading. In this patient several factors may have led to the earlier decrease in arterial O<sub>2</sub> saturation during suspension of breathing.

If the patient were anoxicemic at the start, his arterial O<sub>2</sub> saturation would be on the steeply sloping part of the O<sub>2</sub> dissociation curve and a small decrease in arterial O<sub>2</sub> pressure would cause relatively large changes in saturation. However, our patient did not appear to be anoxicemic initially, as judged by two observations made upon him when he was standing. First, he was able to hold his breath for twenty-six seconds without measurable decrease in arterial O<sub>2</sub> saturation. Second, his arterial O<sub>2</sub> saturation increased the normal amount (4 per cent) when he was given O<sub>2</sub> to breathe instead of air.<sup>3,4</sup>

If the patient had an unusually small functional residual capacity his alveolar and arterial O<sub>2</sub> pressure would fall more rapidly when he stopped breathing. Thus if his functional residual capacity were only 1,200 ml. and his O<sub>2</sub> uptake were 360 ml./minute, his arterial O<sub>2</sub> pressure could fall from 100 mm. to 64 mm. in ten seconds; this would account for the observed decrease in arterial O<sub>2</sub> saturation. We favor this explanation for it is likely that his functional residual capacity was greatly reduced by the force of gravity effecting an unusual elevation



of the weakened diaphragm. The effect of the supine position upon our patient would then be similar to that of a healthy person holding his breath in the position of maximal expiration with additional elevation of the diaphragm such as might be produced by a tight abdominal binder.

Absence of pulmonary ventilation undoubtedly resulted in accumulation of CO<sub>2</sub> in addition to producing anoxemia. The combination of these must have produced intense direct and reflex stimulation of the respiratory center. Dyspnea probably occurred early in our patient because the reduced number of motor units in the diaphragm were required to do an excessive amount of work at this time. A similar situation occurs in patients with poliomyelitis involving the respiratory muscles; in these patients the effort involved merely in breathing through light rubber valves may produce moderate dyspnea.

#### SUMMARY

A man of twenty-eight who had developed urticaria after tetanus antitoxin eighteen years before was given another injection of tetanus antitoxin on August 4, 1947.

Six days later he began to have pain in the

shoulders, arms and upper dorsal region. Ten days after the injection he began to have difficulty in breathing especially when he lay down. Various measurements indicated that he had weakness of his respiratory muscles and that his respiratory symptoms were not psychogenic (as had been suspected at first).

Recovery began in six months and was practically complete in two years. Two and a half years after the onset measurements of his respiratory power showed figures within normal limits and he felt capable of returning to athletics.

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# The American Journal of Medicine

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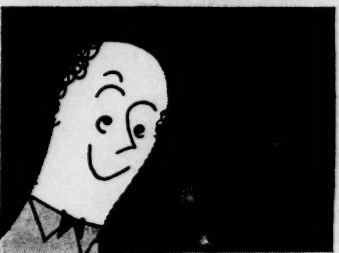
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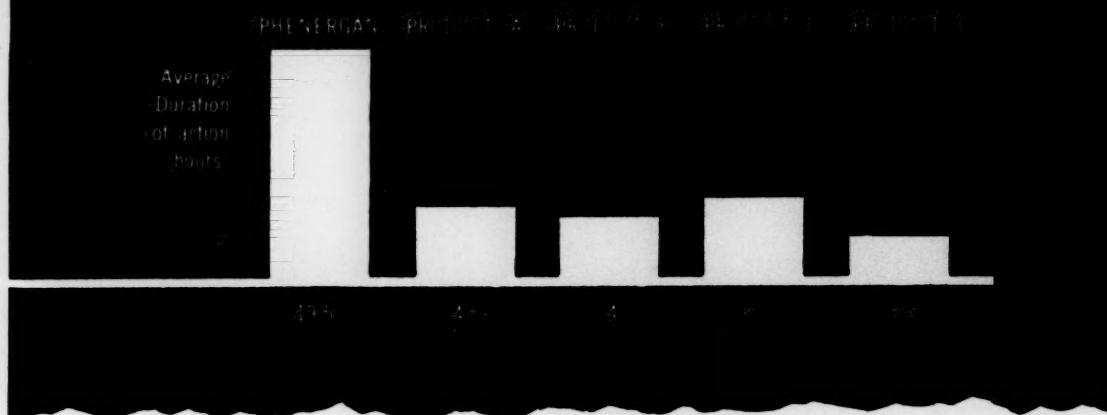
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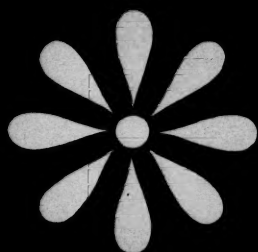
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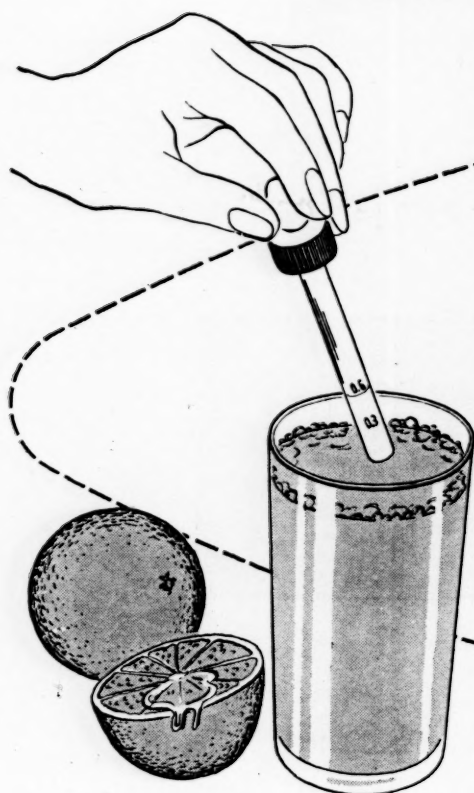


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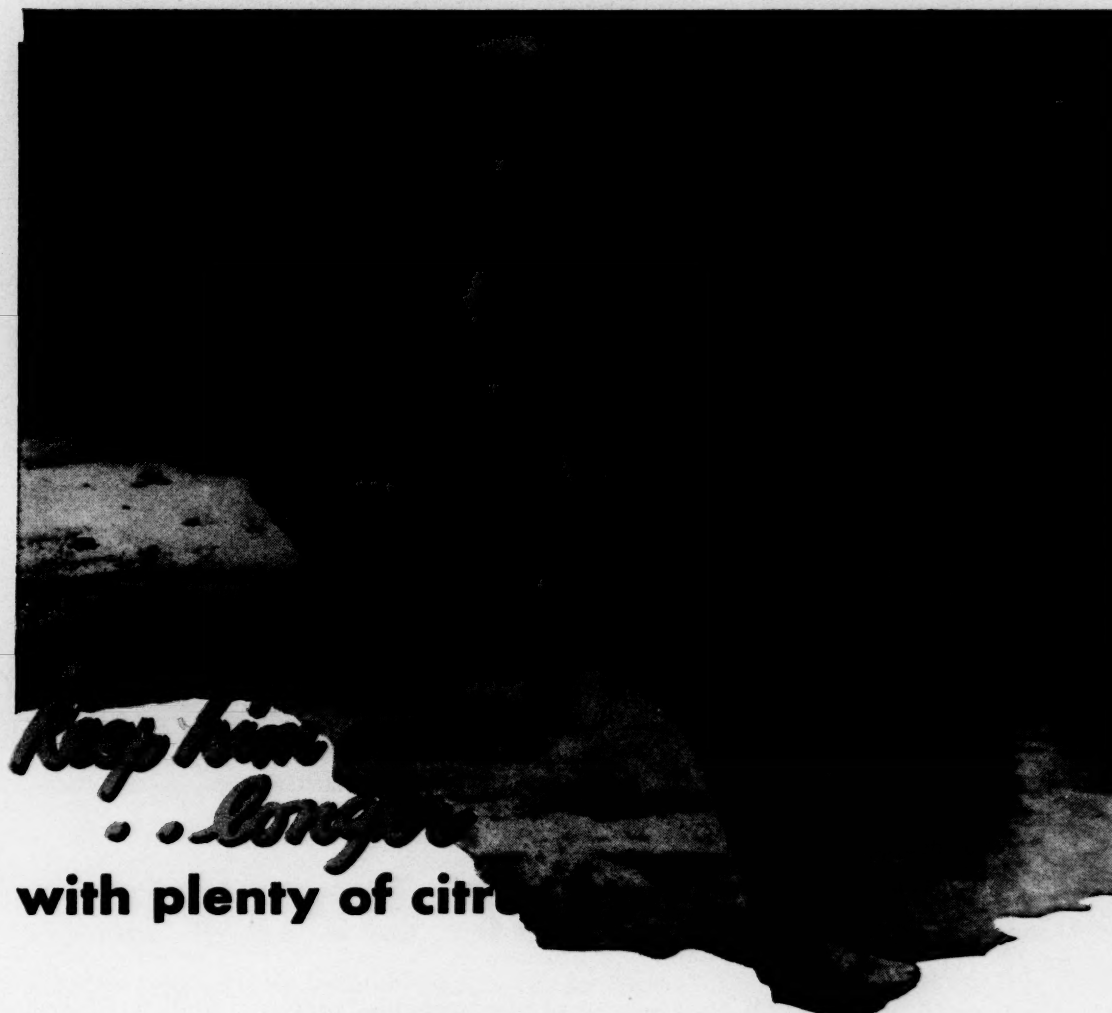
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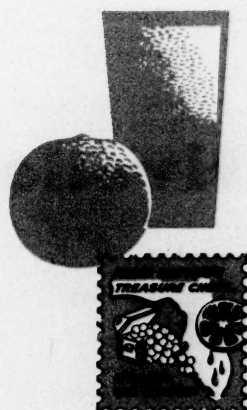
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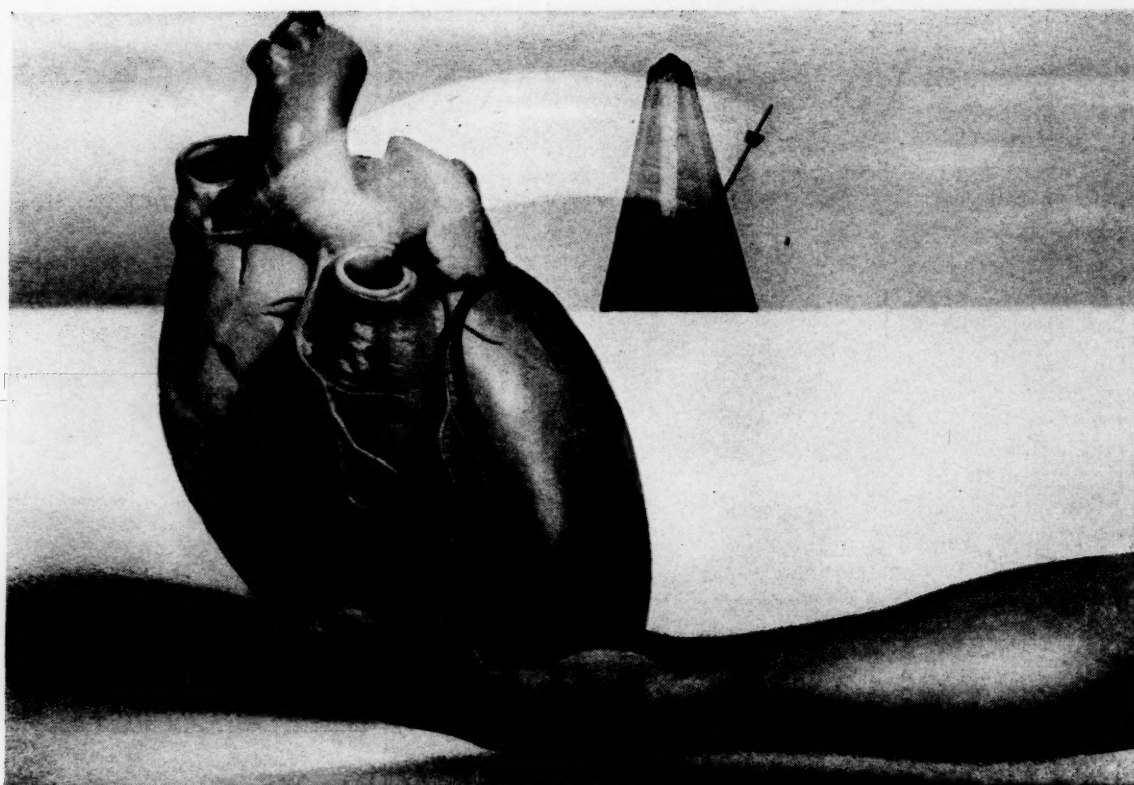
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REFERENCES: 1. Chapman, W. P., Rowlands, E. N., and Jones, C. M.: *New England J. Med.*, 249:1, 1950. 2. Kramer, P. and Ingelfinger, F. J.: *Med. Clin. North America*, 33:1237, 1948. 3. Foosey, E. L., Bergen, J. A., and Dearing, W. H.: *Gastroenterol.*, 11:344, 1948.

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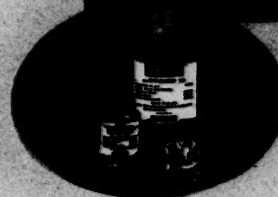
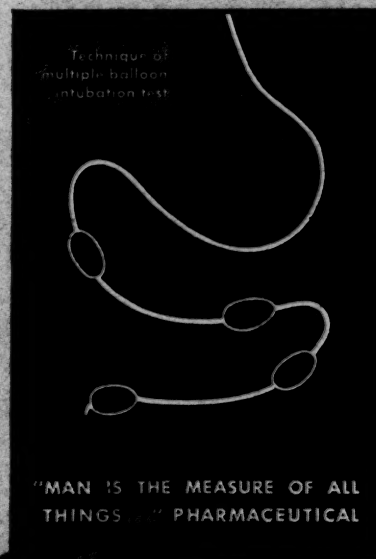
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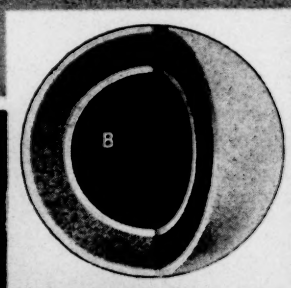
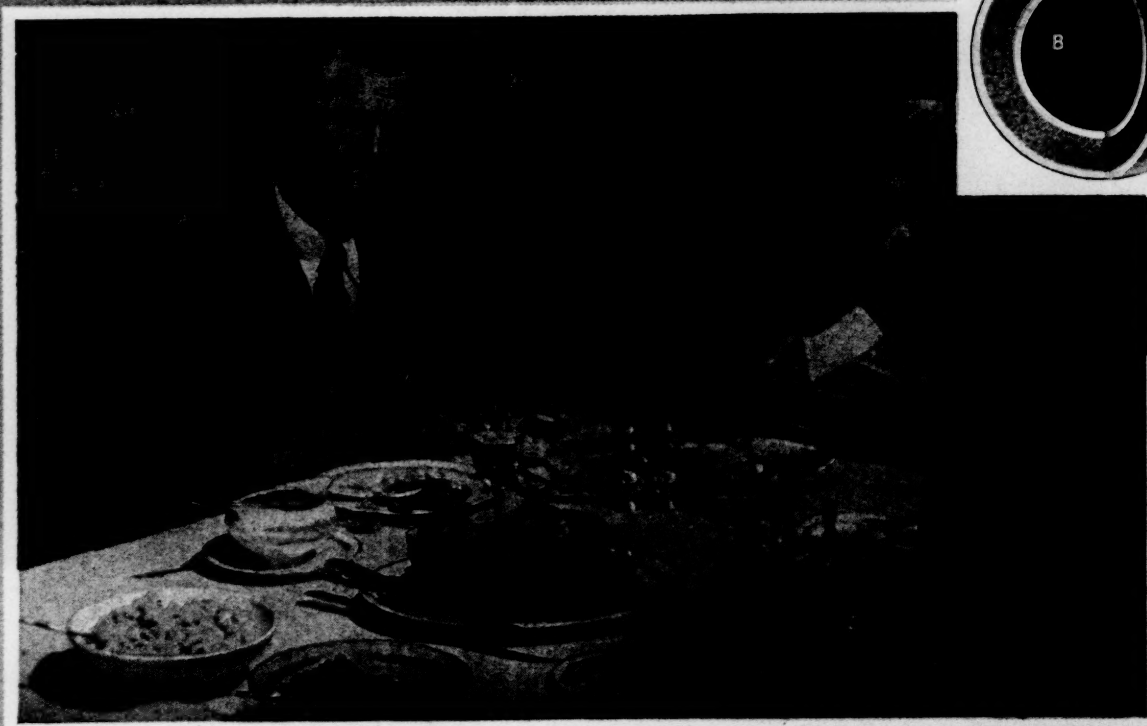
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A suspension of Crystalline Terramycin Hydrochloride in a petrolatum base. One Gm. of ointment provides 1 mg. of Terramycin hydrochloride. Available in tubes containing  $\frac{1}{8}$  oz.



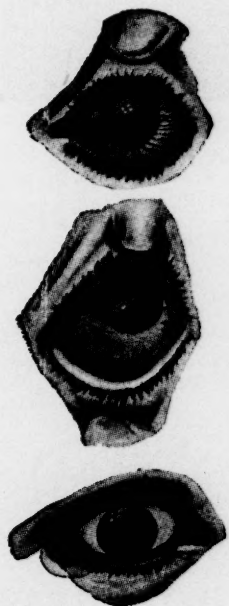
## CRYSTALLINE Terramycin

HYDROCHLORIDE

*Ophthalmic Solution*

Supplied as a dry mixture of Crystalline Terramycin Hydrochloride and a sodium borate-sodium chloride buffer for preparation of topical solutions. Each 5 cc. vial provides 25 mg. of Terramycin to be dissolved in 5 cc. of Water for Injection, U.S.P. Solutions are isotonic with lacrimal fluid and buffered to pH 8.2.

In deep-seated and systemic infections, local treatment is recommended as an adjunct to oral Terramycin therapy.



**Pfizer**

*Antibiotic Division*  
CHAS. PFIZER & CO., INC.  
Brooklyn 6, N. Y.





*Since the first of June*

this new Upjohn plant has  
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It is the culmination of  
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four years of building.  
These greatly expanded  
Upjohn facilities keep pace  
with rapid advances in  
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**Upjohn**

*Medicine...Produced with care...Designed for health*

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

Here is a more  
complete  
solution to  
the weight  
reduction  
problem...

THE 60-10-70 DIET

THIS PLAN

*Plus Obedrin*

60-10-70 DIET

NAME \_\_\_\_\_

WEIGHT \_\_\_\_\_

DATE \_\_\_\_\_

DO NOT EAT EVEN SMALL AMOUNTS OF ANY FOOD NOT ON THIS LIST

**BREAKFAST**

Choose only one item on this list. No Sugar — No Butter.

Small orange  
Orange juice, 1/2 glass (1 oz.)  
1 Medium peach  
Pineapple (1 slice or 1/2 cup, shredded)  
Plums, fresh, 3  
Tangerines, 2

Add any one item on this list.

Bread, 1 slice (white, rye, or whole wheat)  
Graham crackers, 1  
Soda crackers, 10

Choose one beverage. Serve with sugar—unlimited.

Tea or coffee, no cream, no sugar—unlimited  
Skimmed milk—1 glass

Apple juice, 1/2 glass (1 oz.)  
Apple sauce, 1/2 cup  
Cantaloupe or honeydew, 1/2 melon  
Grapes, 1/2 (4 inch)

Doughnut, 1  
Hominy, cooked, 1/2 cup  
Rice, 1/2 cup  
1 Egg (poached or boiled)

**LUNCH**

Choose one, either meat or fish, not both.

1 slice = 4 x 1 inches and 1/2" thick

Kidney, 1/2 cup  
Liver, 1 slice  
Veal, 1 slice  
Hamburger (small cake)  
Beef (lean, beef chuck), 1  
Chicken, ground, 1/2 cup  
Corned beef, 2 slices

Chipped beef, 1 cup  
Lamb chops, lean, 1  
Corned beef, 2 slices

Choose one, either meat or fish, not both.

1 slice = 4 x 1 inches and 1/2" thick

Beef, 2 slices  
Chicken, 1/2 cup  
Corned beef, 2 slices  
Shrimp, 1/4 cup  
Scallops, 1 cup

Copyright 1950 by The S. E. Massengill Company

#### FORMULA

Semoxydrine  
Hydrochloride..... 5 mg.  
Pentobarbital Sodium 20 mg.  
Ascorbic Acid..... 100 mg.  
Thiamine  
Hydrochloride..... 0.5 mg.  
Riboflavin..... 1 mg.  
Niacinamide..... 5 mg.

Obedrin is supplied in bottles of 100, 500, and 1,000 yellow grooved tablets.



SEND FOR YOUR COMPLIMENTARY  
COPY OF 60-10-70  
DIET SHEETS TODAY

#### CURBS THE APPETITE

Through the use of the unique 60-10-70 diet and Obedrin tablets, considerable weight can be lost without troublesome hunger or impairment of nitrogen balance. Patient cooperation is assured because morale is kept high and excessive fatigue due to a nutritionally unsound diet is avoided.

#### MAINTAINS GOOD NUTRITION

The 60-10-70 diet allows free choice of many foods and supplies 70 Gm. of protein, 60 Gm. of carbohydrate, and 10 Gm. of fat, approximately 610 calories. The diet sheets are complete and self-explanatory, making it easy for the patient to do his share.

Obedrin permits adequate dosage of Semoxydrine Hydrochloride (methamphetamine) to suppress appetite. The corrective dose of pentobarbital cancels excessive central nervous stimulation, while vitamins help maintain the patient's sense of well-being.

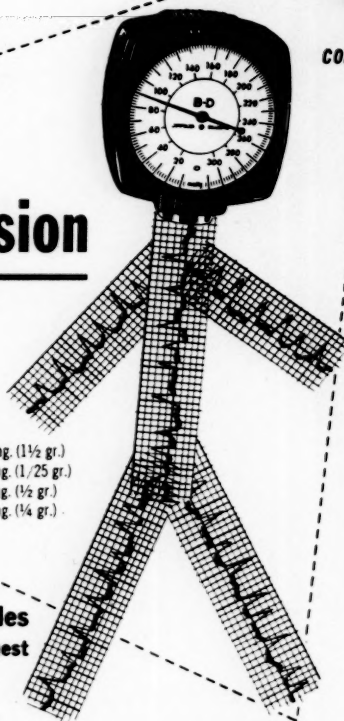
THE S. E. MASSENGILL COMPANY

Bristol, Tenn.-Va.

NEW YORK • SAN FRANCISCO • KANSAS CITY

*Obedrin*

improves the  
**whole**  
patient in  
**hypertension**



Each PERTENAL tablet contains:  
Veratrum Viride ..... 100 mg. (1½ gr.)  
Homatropine Methyl Bromide. 2.5 mg. (1/25 gr.)  
Mannitol Hexanitrate ..... 30 mg. (½ gr.)  
Phenobarbital ..... 15 mg. (¼ gr.)

**PERTENAL samples**  
on request

# PERTENAL

*controls pressure and symptoms that send pressure soaring*

**more normal pressure**  
around the clock with two potent vasodilators.

**eases stress on heart**  
by decreasing peripheral resistance.

**relieves gastro-intestinal spasm**  
pain and other discomforts which aggravate pressure.

**relaxes patient**  
mentally, physically; allays tension, worry, restlessness, insomnia.

**from the first day of PERTENAL**  
*therapy the whole patient is more comfortable, happier; able to live a more normal, perhaps longer life.*

CROOKES LABORATORIES, INC.



305 EAST 45 ST., NEW YORK, N. Y.

# Erythgen®

TABLETS

*The Practical Oral  
Anti-Anemia Preparation  
for Day to Day Use*

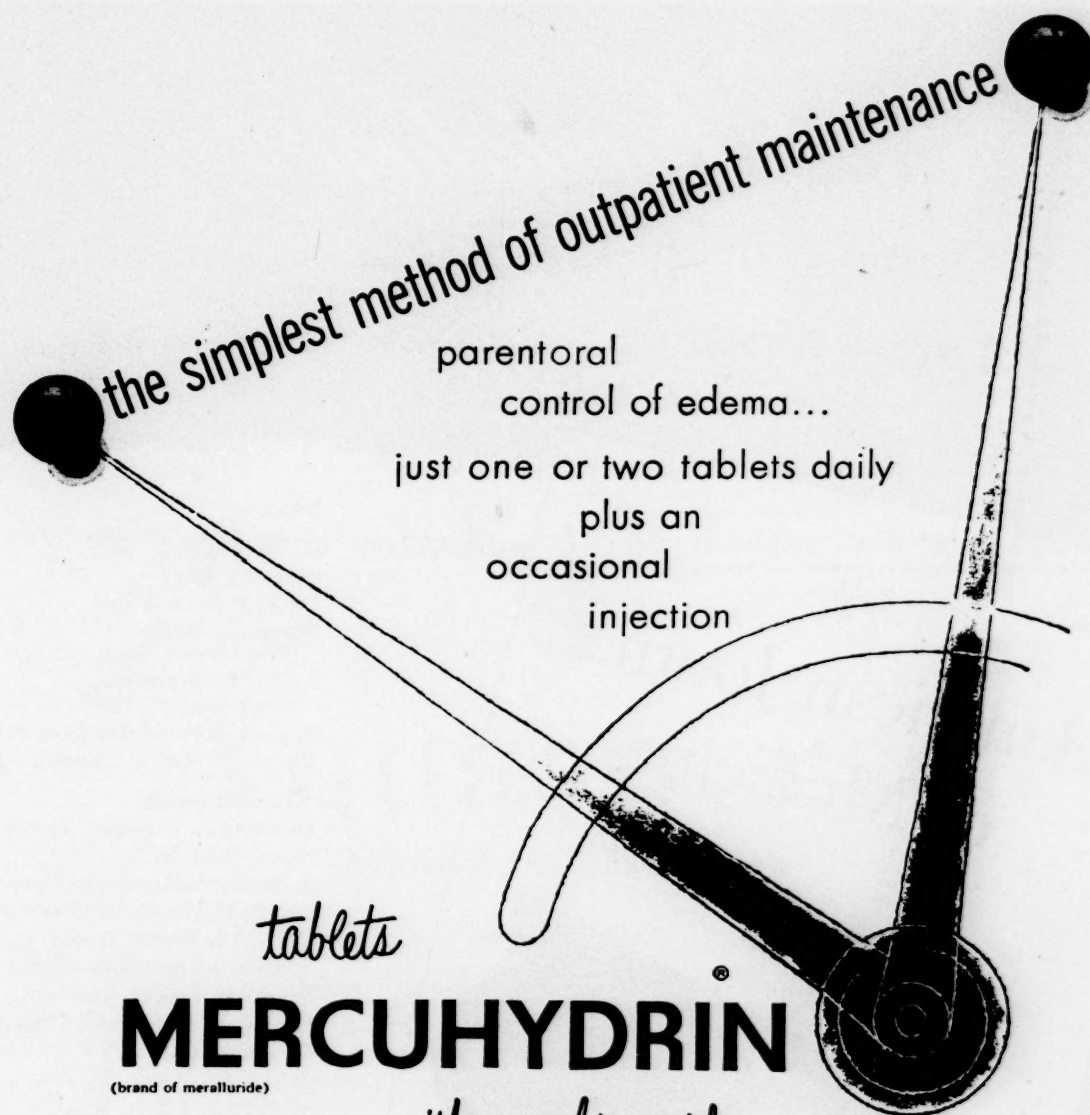
Bottles of 100, 1,000

- Provides a balanced formula of Vitamin B<sub>12</sub>, Ferrous Iron, B Complex Vitamins, Vitamin C.
- Therapeutically efficacious in widely separated groups of anemias . . . both macrocytic and microcytic.
- 6 tablets daily supply therapeutic quantities of B<sub>12</sub> and Iron, and minimum daily requirements (National Research Council) of B Vitamins and Vitamin C.

*G. W. Carrick Co.*

NEWARK 1, NEW JERSEY





# MERCUHYDRIN<sup>®</sup>

(brand of meralluride)

*with ascorbic acid*

## ORAL MERCURIAL DIURETIC

To secure the greatest efficacy and all the advantages of Tablets MERCUHYDRIN with Ascorbic Acid, a three-week initial supply should be prescribed . . . . . 25 to 50 tablets.

**dosage:** One or two tablets daily—morning or evening—preferably after meals.

**available:** Bottles of 100 tablets. Each tablet contains meralluride

60 mg. (equivalent to 19.5 mg. mercury) and ascorbic acid 100 mg.

*L*akeside  
laboratories, INC., MILWAUKEE 1, WISCONSIN

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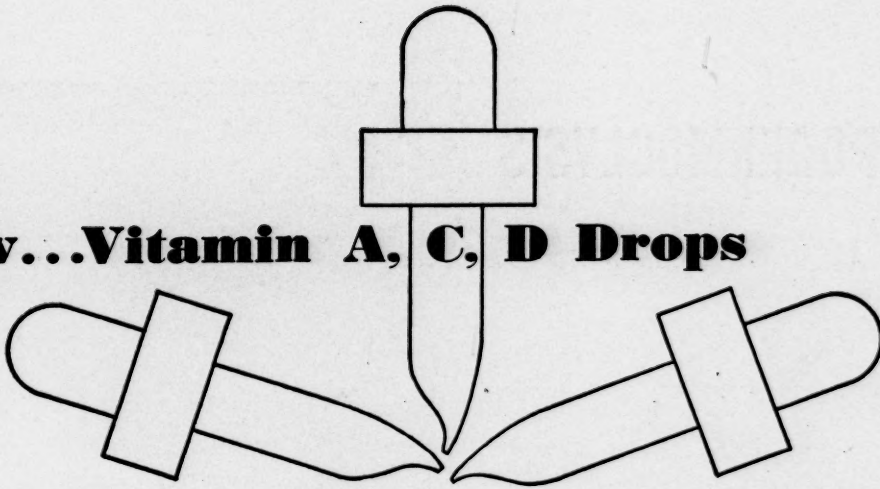
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**in aqueous solution for better absorption**

# Aquasperse

## Vitamin ACD Drops

### Advantages:

**Aqueous Solution**—means faster and more efficient absorption of the fat-soluble vitamins A and D.

In conditions in which fat absorption is impaired, such as diarrheas, celiac disease, hepatic and biliary disturbances, the value of an aqueous solution is obvious.

**Hypoallergenic**—all the component vitamins of Aquasperse are synthetic. Consequently it may be used where patients cannot tolerate natural source vitamins.

**Pleasant flavor... no objectionable odor**—Aquasperse has an appealing, slightly citrus flavor and practically no odor.

### EACH 0.6 CC. CONTAINS:

vitamin A.....	5000 U.S.P. Units
vitamin D <sub>3</sub> .....	1000 U.S.P. Units
ascorbic acid.....	50 mg.

*Note:* The vitamin D<sub>3</sub> in Aquasperse is chemically identical and biologically equivalent to the vitamin D of cod liver oil.

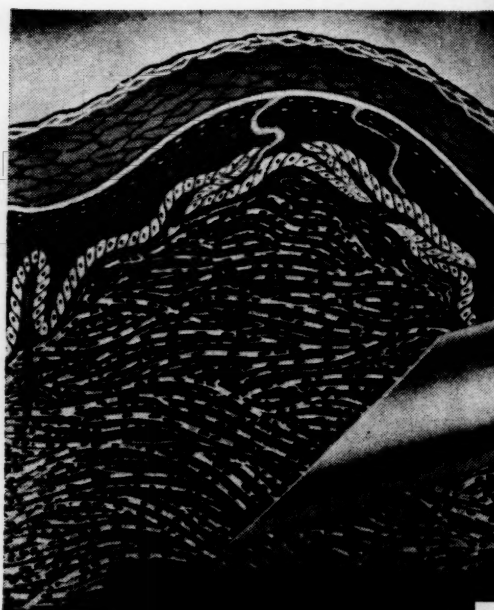
**Available**—In bottles of 15 cc. and 50 cc. (with calibrated dropper)

**WHITE LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.**



# HYPODERMOCLYSIS

with WYDASE



without WYDASE

## WYDASE

(formerly Hydase)

Lyophilized Hyaluronidase

*Wyeth*

Highly  
Purified

*For speedy absorption of fluids in hypodermoclysis. Prevents pain from stretching of tissue—nontoxic and apparently nonallergenic.*

*For More Complete and Widespread Local Anesthesia—fewer injections of local anesthetics required.*

WYDASE in dry form is stable indefinitely; keeps in sterile solution for 2 weeks—refrigeration unnecessary.

SUPPLIED: Vials of 150 and 500 turbidity reducing (TR) units.

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